452. *Acyl Isothiocyanates. Part III.*[1] *Properties of Some Phosphoroisothiocyanatidates.*

By D. T. Elmore and J. R. Ogle.

Diphenyl phosphoroisothiocyanatidate affords good yields of addition products with amines, methanol, and methanethiol. Some *N*-diphenoxyphosphinylthioureas are remarkably sensitive to hydrolysis, and possible mechanisms are considered. Addition and substitution are competitive when amines react with diethyl phosphoroisothiocyanatidate, but the controlling factors have not been satisfactorily elucidated. Attempts to prepare dibenzyl phosphoroisothiocyanatidate and its derivatives are described.

Earlier papers in this series [1,2] have described some of the chemistry of simple acyl isothiocyanates. Depending on various conditions mentioned therein, reaction of these compounds with nucleophiles may occur in either of two ways; addition to the isothiocyanate group affords *N*-acylthiocarbamoyl compounds, whereas substitution at the carbonyl-carbon atom gives *N*-acyl derivatives. In the present paper, we record some experiments with phosphorus-containing isothiocyanates. Phosphorous and phosphoric tri-isothiocyanates were the subject of early studies by Miquel and by Dixon,[3] but interest in isothiocyanates of phosphorus has revived only in the last decade with the synthesis of esters (I) of phosphoroisothiocyanatidic acid. The diethyl ester (I; R = Et) was the first compound of this type to be prepared,[4,5] but the reported properties were not consistent. This discrepancy has been resolved by more recent studies,[6,7] as well as by the present work. The diphenyl ester (I; R = Ph) was prepared by Kenner, Khorana, and Stedman,[8] and several other aryl derivatives are now known.[6,7] Phosphoroisothiocyanatidates have commonly been prepared by treatment of phosphorochloridates in a suitable solvent with potassium thiocyanate,[4,5,7,8] and the latter also reacts with tetraphenyl pyrophosphate to give diphenyl phosphoroisothiocyanatidate.[8] Michalski and Wieczorkowski [6] have recently

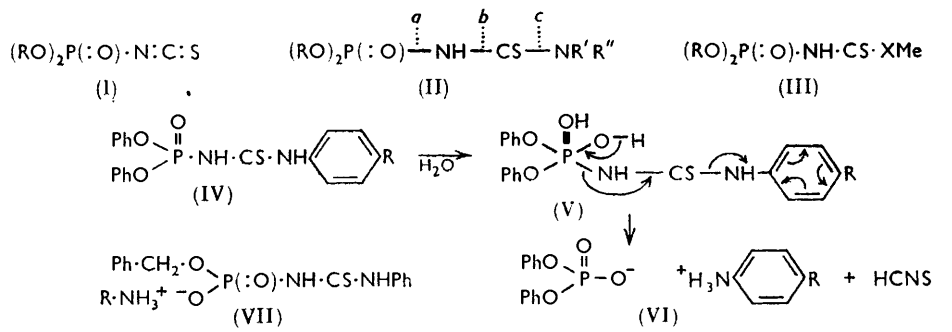
[1] Part II, Elmore and Ogle, *J.*, 1958, 1141.
[2] Elmore, Ogle, Fletcher, and Toseland, *J.*, 1956, 4458.
[3] Miquel, *Ann. Chim. Phys.*, 1877, **11**, 341; Dixon, *J.*, 1901, **79**, 541; Dixon and Taylor, *J.*, 1908, **93**, 2148; Dixon, *J.*, 1904, **85**, 350.
[4] Saunders, Stacey, Wild, and Wilding, *J.*, 1948, 699.
[5] Cook, Ilett, Saunders, Stacey, Watson, Wilding, and Woodcock, *J.*, 1949, 2921.
[6] Michalski and Wieczorkowski, *Roczniki Chem.*, 1955, **29**, 137; 1957, **31**, 585.
[7] Leuchenko and Zhmurova, *Ukrain. khim. Zhur.*, 1956, **22**, 623.
[8] Kenner, Khorana, and Stedman, *J.*, 1953, 673.

devised a novel synthesis, which involves the oxidation of dialkyl phosphites with thiocyanogen; this recalls the preparation of phosphorochloridates by chlorination of phosphite diesters.[9]

Phosphoroisothiocyanatidates have been reported to react additively with amines [6,7,8] and alcohols.[10] We have found that diphenyl phosphoroisothiocyanatidate in inert solvents reacts additively with a variety of amines to give the corresponding thioureas (II) in good yield. Since diphenyl phosphoroisothiocyanatidate in aqueous dioxan at pH 8·5 was hydrolysed completely within 5 min., experiments, similar to those between benzoyl isothiocyanate and amino-acids in aqueous solution,[1] were precluded. The consumption of 2 moles of alkali per mole of isothiocyanatidate at constant pH, however, indicated that hydrolysis comprised only a nucleophilic attack at the phosphorus atom, in contrast to the behaviour of benzoyl isothiocyanate.[1] It thus appears that diphenyl phosphoroisothiocyanatidate is intermediate in properties between aliphatic and aromatic acyl isothiocyanates.

Methanol and methanethiol afforded the expected thioncarbamate (III; R = Ph, X = O) and dithiocarbamate (III; R = Ph, X = S) respectively. The latter was of interest as a potential reagent for procuring the stepwise degradation of peptides from the *N*-terminus.[2,11] It reacted rapidly with glycine ethyl ester in ethanol to give *N*-diphenoxyphosphinylthiocarbamoylglycine ethyl ester (II; R = Ph, R′ = $CH_2 \cdot CO_2Et$, R″ = H), identical with a sample prepared directly from the phosphoroisothiocyanatidate and glycine ethyl ester. Similar reactions with glycylglycine ethyl ester afforded only intractable gums, which appeared to contain the expected product, but could not be purified. Hot, dilute acids degraded the glycine derivative (II; R = Ph, R′ = $CH_2 \cdot CO_2Et$, R″ = H) to 2-thiohydantoin in low yield, while the gummy product from the peptide ester broke down in acids in a complex manner, and only traces of 2-thiohydantoin were detected. A possible explanation of these observations lies in the peculiar lability to hydrolysis of the *N*-diphenoxyphosphinyl group in certain thioureas discussed below. These results, together with the insolubility of the dithiocarbamate, discouraged us from further examination of its possible use as a reagent in the stepwise degradation of peptides.

We were surprised to find that *N*-aryl-*N*′-diphenoxyphosphinylthioureas were extremely readily hydrolysed. For example, *p*-(*N*-diphenoxyphosphinylthiocarbamoyl)-aminobenzoic acid (IV; R = *p*-CO_2H) or its ethyl ester, which were obtained by reaction of diphenyl phosphoroisothiocyanatidate and *p*-aminobenzoic acid in dry ether or ethyl



p-aminobenzoate in dry acetonitrile, was quantitatively and rapidly converted into *p*-carboxyanilinium or *p*-ethoxycarbonylanilinium diphenyl phosphate during attempted recrystallisation from aqueous ethanol. *N*-Diphenoxyphosphinyl-*N*′-phenylthiourea survived this treatment, but was hydrolysed to anilinium diphenyl phosphate after 8 hr. in

[9] McCombie, Saunders, and Stacey, *J.*, 1945, 380; Atherton, Openshaw, and Todd, *ibid.*, p. 382.
[10] Zhmurova, *Ukrain. khim. Zhur.*, 1956, **22**, 627.
[11] Elmore and Toseland, *J.*, 1954, 4533.

refluxing water. In contrast, *p*-(*N*-benzoylthiocarbamoyl)aminobenzoic acid and *N*-cyclohexyl-*N'*-diphenoxyphosphinylthiourea were stable under these conditions. It appears from these results that the diphenoxyphosphinyl group has some characteristic, not possessed by the benzoyl group, which promotes lability to hydrolysis. An electron-attracting group at the other end of the molecule also appears to be necessary. In addition to the above products, thiocyanate ion (approximately 0·9 equivalent) was found in the hydrolysate of the thiourea (IV; R = CO_2Et). Hydrogen sulphide, an expected breakdown product of thiocyanic acid, was also usually evolved. Several reaction mechanisms are possible, and these may occur concurrently, especially since the pH drops during reaction. Hydrolysis of the thioureas (II; R = Ph, R' = aryl, R'' = H) may occur at *a*, *b*, or *c*. While we cannot be certain of the mechanism in absence of a kinetic investigation, we propose that, by using the *d*-orbitals of phosphorus, a molecule of water is added, and this step is followed by a synchronous cleavage at both *a* and *c*, as recently suggested by Grob [12] to explain the cleavage of certain γ-aminoalkyl halides. A synchronous mechanism is preferred, since the $\rangle N{\cdot}CS{\cdot}N\langle$ system is planar. The mechanism also requires the simultaneous action of electron-donating and electron-attracting groups at opposite ends of the molecule. The tendency of the intermediate (V) to lose a proton might provide the former, while the latter influence could be derived from the electromeric effects of the aromatic ring. Replacement of this by the electron-donating cyclohexyl group would explain the stability of *N*-cyclohexyl-*N'*-diphenoxyphosphinylthiourea. This mechanism accounts for the formation of thiocyanate ion and diphenyl phosphate. It appears that inductive electron-withdrawal is also effective, since *N*-diphenoxyphosphinylthiocarbamoylsarcosine *p*-toluidide (II; R = Ph, R' = Me, R'' = $CH_2{\cdot}CO{\cdot}NH{\cdot}C_6H_4Me$-*p*) was completely hydrolysed by boiling aqueous dioxan in 15 min. It is worth noting that *N*-diphenoxyphosphinylthiocarbamoyl derivatives of amino-acids, if they were readily available, would be useful compounds for peptide synthesis, since the protecting group could be removed under very mild conditions. A number of simple *N*-acylthiocarbamoylamino-acids have been converted into amides by standard procedures for peptide synthesis.[13]

Nucleophilic attack by a water molecule at the phosphorus atom of the *N*-diphenoxyphosphinylthioureas (IV) could result in cleavage of the P–N bond and lead to diphenyl phosphate and a thiourea, which might be further hydrolysed under the acidic conditions. For example, we found that after equimolar quantities of diphenyl phosphate and *N*-phenylthiourea had been heated in refluxing water for 8 hr., only 30% of the thiourea could be recovered; in addition, anilinium diphenyl phosphate (23%) was isolated and thiocyanate ions were present in solution. Since, under similar conditions, *N*-diphenoxyphosphinyl-*N'*-phenylthiourea afforded 84% of the theoretical yield of anilinium diphenyl phosphate, the above mechanism can make only a minor contribution. Nucleophilic attack of water molecules at the thiocarbonyl-carbon atom could theoretically result in cleavage at either *b* or *c*. Both mechanisms are considered unlikely, since in each case one product would be diphenyl phosphoramidate, and it is unlikely that this would be hydrolysed to any appreciable extent under the conditions of hydrolysis of, *e.g.*, *p*-(*N*-diphenoxyphosphinylthiocarbamoyl)aminobenzoic acid.

The physical properties of our sample of diethyl phosphoroisothiocyanatidate were in accord with those most recently described.[6,7] Moreover, the presence in the infrared spectrum of a broad band at 1980—2050 $cm.^{-1}$ with a shoulder at *ca.* 2070 $cm.^{-1}$, similar to those observed for alkyl isothiocyanates, diphenyl phosphoroisothiocyanatidate, and benzoyl isothiocyanate,[14] reinforces the conclusion of Michalski and Wieczorkowski,[6] based on molar refractivity measurements, that the compound is an isothiocyanate rather than a

[12] Grob, *Helv. Chim. Acta*, 1955, **38**, 594; *Experientia*, 1957, **13**, 126; Kekulé Symp. Theor. Org. Chem., London, Butterworths, 1958.
[13] Elmore and Toseland, *J.*, 1957, 2460.
[14] Lieber, Rao, and Ramachandran, *Spectrochim. Acta*, 1959, **13**, 296; Elmore and Ogle, unpublished observations.

thiocyanate. We attribute the low frequency of the isothiocyanate band to conjugation with the P=O group. Although diethyl phosphoroisothiocyanatidate afforded crystalline thioureas after reaction with a variety of amines, yields were usually less than 50% of theoretical, and we believe that nucleophilic substitution at the phosphorus atom competes strongly with addition at the isothiocyanate group. In order to gain insight into the factors controlling the relative rates of the competing reactions, we allowed the phosphoroisothiocyanatidate in benzene or acetonitrile to react with aniline, ethylamine, cyclohexylamine, and t-butylamine under standard conditions and determined the ratio of thiourea to thiocyanate ion formed. The results were disappointing, since, although we could usually account for 100 ± 5% of reactant used, yields were rather variable under a particular set of conditions and not very sensitive to change of base or solvent.

[*Note Added, April 27th*, 1959.—Very recently, Kulka (*Canad. J. Chem.*, 1959, **37**, 525) has reported that diethyl phosphoroisothiocyanatidate is readily decomposed to ethyl thiocyanate. The physical properties of our preparation agree closely with those recorded by Kulka, but it is possible that our sample had partially decomposed on storage. This would explain, o some extent, the low yields of addition products with amines and would mask effects due to change of base and solvent.]

The preparation of dibenzyl phosphoroisothiocyanatidate, as expected, presented considerable difficulty. The ready monodebenzylation of dibenzyl phosphorochloridate by tertiary bases has already been observed,[15] and our own experience in the synthesis of benzyloxycarbonyl isothiocyanate [2] confirmed earlier reports [16] on the ease with which benzyl esters are attacked by thiocyanate ions. Accordingly, reaction between potassium thiocyanate and dibenzyl phosphorochloridate was conducted in a mixture of carbon tetrachloride and acetonitrile at −20°, but the rate of formation of isothiocyanatidate appeared to be inconveniently slow. Oxidation of dibenzyl phosphite with thiocyanogen seemed a more attractive approach, but numerous experiments revealed its capriciousness. No attempt was made to isolate the phosphoroisothiocyanatidate, and addition of aniline consistently afforded the *O*-benzyl-*N*-phenylthiocarbamoylphosphoramidic acid [isolated as its cyclohexylammonium (VII; R = C_6H_{11}) or anilinium (VII; R = Ph) salts] in 10—15% yield. Presumably, monodebenzylation was effected by thiocyanate ions. After oxidation of dibenzyl phosphite at −10°, *N*-dibenzyloxyphosphinyl-*N'*-phenylthiourea (II; R = Ph·CH_2, R' = Ph, R'' = H) was isolated. Several experiments using cyclohexylamine and methanethiol gave no crystalline addition products.

Experimental

Diphenyl phosphoroisothiocyanatidate (I; R = Ph) was prepared by a modification of the method of Kenner *et al.*; [8] the volume of acetonitrile was reduced to one-fifth of that previously used. The mixture was heated under reflux for 30 min., cooled to 0°, and filtered without addition of benzene. After removal of solvent, the product was purified by distillation at 0·01 mm. (bath-temp. 210—230°) or by short-path distillation at 130—140°/0·001 mm., then having n_D 1·5840. The isothiocyanate group gave rise to a broad peak at 1970—2040 cm.$^{-1}$ with a shoulder at *ca.* 2120 cm.$^{-1}$ in the infrared spectrum.

Methyl N-*Diphenoxyphosphinylthioncarbamate* (III; R = Ph, X = O).—Diphenyl phosphoroisothiocyanatidate (1 g.) was heated in methanol (5 c.c.) for 2 hr. Evaporation of solvent under reduced pressure afforded the hygroscopic thioncarbamate (0·9 g.), which had m. p. 129—130° after recrystallisation from ethyl acetate–light petroleum (b. p. 40—60°) (Found: C, 52·2; H, 4·4; N, 4·6; P, 10·1; S, 9·6. Calc. for $C_{14}H_{14}O_4NSP$: C, 52·0; H, 4·4; N, 4·3; P, 9·6; S, 9·9%). Zhmurova [10] records m. p. 132—134°.

Methyl N-*Diphenoxyphosphinyldithiocarbamate* (III; R = Ph, X = S).—(*a*) Diphenyl phosphoroisothiocyanatidate (7·25 g.) and methanethiol (5 g.) were kept in acetonitrile (50 c.c.) for 5 days at room temperature. The *dithiocarbamate*, which separated when the mixture was

[15] Atherton, Howard, and Todd, *J.*, 1948, 1106; Baddiley, Clark, Michalski, and Todd, *J.*, 1949, 815; Clark and Todd, *J.*, 1950, 2023.
[16] Morrison and Atherton, B.P., 675, 779.

poured into a large volume of water, was recrystallised from ethyl acetate–light petroleum (b. p. 40—60°) and then had m. p. 133—134° (Found: C, 50·0; H, 4·2; P, 9·6. $C_{14}H_{14}O_3NS_2P$ requires C, 49·6; H, 4·2; P, 9·2%).

(*b*) Diphenyl phosphorochloridate (13·4 g.) and potassium thiocyanate (5·0 g.) were heated in acetonitrile (50 c.c.) for 30 min. After cooling, methanethiol (5 g.) was added and the solution was kept for 5 days at room temperature. Isolation as before afforded the product (8·5 g.) with identical m. p.

N-*Diphenoxyphosphinyl*-N′-*phenylthiourea* (IV; R = H).—This was prepared as described by Leuchenko and Zhmurova,[7] and by a method similar to (*b*) for the dithiocarbamate above. Recrystallised from aqueous ethanol it had m. p. 144—145°, whereas Leuchenko and Zhmurova [7] record m. p. 143—144° (Found: C, 59·5; H, 4·9; N, 7·5; P, 7·9; S, 8·4. Calc. for $C_{19}H_{17}O_3N_2SP$: C, 59·4; H, 4·5; N, 7·3; P, 8·1; S, 8·4%). The thiourea (0·2 g.) gradually dissolved in refluxing water (10 c.c.) during 8 hr. On cooling, anilinium diphenyl phosphate (0·15 g.) separated and had m. p. 165·5—166·5°, undepressed on admixture with synthetic material.

Hydrolysis of N-*Phenylthiourea.*—*N*-Phenylthiourea (0·152 g.) and diphenyl phosphate (0·25 g.) were heated in water (10 c.c.) under reflux for 8 hr. On cooling, anilinium diphenyl phosphate (0·08 g.) crystallised, and had m. p. and mixed m. p. 164—165° after recrystallisation from water. *N*-Phenylthiourea (0·045 g.) was recovered from the mother-liquors.

N-*Diphenoxyphosphinyl*-N′-p-*nitrophenylthiourea* (IV; R = NO_2).—This *compound* (2·82 g.) was obtained by interaction of diphenyl phosphoroisothiocyanatidate (2·91 g.) and *p*-nitroaniline (1·38 g.) in benzene (10 c.c.). Recrystallised first from ethyl acetate and then from benzene–light petroleum (b. p. 40—60°), it had m. p. 139—140° (Found: C, 53·2; H, 4·0; N, 9·7; P, 6·7; S, 7·4. $C_{19}H_{16}O_5N_3SP$ requires C, 53·2; H, 3·8; N, 9·8; P, 7·2; S, 7·5%). The thiourea (0·25 g.) was heated under reflux in water for 14 hr. The cooled solution deposited *p*-nitroaniline (0·09 g.), which had m. p. 144—145° alone and in admixture with an authentic sample after recrystallisation from aqueous ethanol. The hydrolysis mother-liquors were strongly acidified and extracted with 4 portions of ethyl acetate. The combined extracts were dried (Na_2SO_4) and evaporated to a gum which was dissolved in benzene. Addition of cyclohexylamine caused cyclohexylammonium diphenyl phosphate to separate in quantitative yield. Recrystallised from ethanol–ether, it had m. p. and mixed m. p. 195·5—196·5°.

p-(N-*Diphenoxyphosphinylthiocarbamoyl*)*aminobenzoic Acid* (IV; R = CO_2H).—Diphenyl phosphoroisothiocyanatidate (2·91 g.) and *p*-aminobenzoic acid (1·37 g.) were kept overnight in ether (300 c.c.). An insoluble material was removed, and the solution was concentrated under reduced pressure to 50 c.c. Addition of light petroleum (b. p. 40—60°) precipitated a gum. Further addition of light petroleum (b. p. 40—60°) to the supernatant liquid and storage at 0° afforded the *thiourea* (1·22 g., 1·71 g., and 2·85 g. in successive experiments); it had m. p. 128—130° and could not be recrystallised owing to its ready decomposition (Found: C, 56·0; H, 4·3; N, 6·9; P, 7·1; S, 7·6. $C_{20}H_{17}O_5N_2SP$ requires C, 56·1; H, 4·0; N, 6·5; P, 7·2; S, 7·5%). The thiourea (0·10 g.) was heated in 50% aqueous ethanol (10 c.c.) under reflux for 15 min. Solvent was removed and the residue of p-*carboxyanilinium diphenyl phosphate* was crystallised from aqueous ethanol. It had m. p. 188—189°, undepressed by admixture with a sample obtained by interaction of *p*-aminobenzoic acid and diphenyl phosphate in dioxan; the two specimens had identical infrared spectra (Found: C, 58·0; H, 4·7; N, 3·6; P, 7·6. $C_{19}H_{18}O_6NP,\frac{1}{2}H_2O$ requires C, 57·6; H, 4·8; N, 3·5; P, 7·8%).

Ethyl p-(N-*Diphenoxyphosphinylthiocarbamoyl*)*aminobenzoate* (IV; R = CO_2Et).—Diphenyl phosphoroisothiocyanatidate (5·82 g.) and ethyl *p*-aminobenzoate (3·36 g.) were kept for 6 hr. in acetonitrile (25 c.c.). The *product* (8·36 g.) separated and was recrystallised from ethyl acetate–light petroleum (b. p. 40—60°); it then had m. p. 126—127° (Found: C, 57·8; H, 4·9; N, 5·6; P, 6·6; S, 7·2. $C_{22}H_{21}O_5N_2SP$ requires C, 57·9; H, 4·6; N, 6·1; P, 6·8; S, 7·0%). Heated in boiling water, this compound (1 g.) dissolved within 20 min., and hydrogen sulphide was evolved. [A separate experiment carried out in dioxan–water (3 : 2) at 100° revealed that approximately 90% of the theoretical amount of thiocyanate ion was liberated within 3 min.] On cooling, a gum separated and was extracted with two portions of ethyl acetate. The combined extracts were dried (Na_2SO_4), evaporated, and treated with light petroleum (b. p. 40—60°). The resulting gum (0·80 g.) solidified at 0° and was recrystallised from aqueous ethanol. The p-*ethoxycarbonylanilinium diphenyl phosphate* had m. p. 98—99°, undepressed by admixture with a sample prepared from ethyl *p*-aminobenzoate and diphenyl phosphate in

benzene; the two specimens had identical spectra (Found: C, 60·6; H, 5·4; N, 3·7. $C_{21}H_{22}O_6NP$ requires C, 60·7; H, 5·3; N, 3·4%).

N-*Diphenoxyphosphinylthiocarbamoylsarcosine* p-*Toluidide* (II; R = Ph, R′ = Me, R″ = CH_2·CO·NH·C_6H_4·Me-*p*).—Sarcosine *p*-toluidide (from 2·59 g. of hydrobromide[17]) and diphenyl phosphoroisothiocyanatidate (2·91 g.) in benzene (20 c.c.) afforded this *compound* (4·5 g.). Recrystallised from ethanol–ethyl acetate and then from ethanol, it had m. p. 141·5—142·0° (Found: C, 58·4; H, 5·3; N, 8·6; P, 6·9; S, 7·2. $C_{23}H_{24}O_4N_3SP$ requires C, 58·8; H, 5·2; N, 9·0; P, 6·6; S, 6·8%). A solution of this compound in dioxan–water (3 : 2) was heated for 15 min. and then evaporated under reduced pressure to a gum. This was separated into basic and acidic fractions by standard methods, and afforded sarcosine *p*-toluidide [61%; isolated as the hydrobromide,[17] m. p. 258—260° (decomp.)] and diphenyl phosphate (75%; isolated as its cyclohexylammonium salt, m. p. and mixed m. p. 195—196°).

N-*Diphenoxyphosphinylthiocarbamoylsarcosine ethyl ester* (II; R = Ph, R′ = Me, R″ = CH_2·CO_2Et) was prepared in the same manner as the *p*-toluidide. Recrystallised from benzene–light petroleum (b. p. 40—60°), it had m. p. 124·5—125·5° (Found: C, 52·6; H, 5·4; N, 6·6; S, 7·5. $C_{18}H_{21}O_5N_2SP$ requires C, 52·9; H, 5·2; N, 6·9; S, 7·9%).

N-*Diphenoxyphosphinylthiocarbamoylglycine Ethyl Ester* (II; R = Ph, R′ = H, R″ = CH_2·CO_2Et).—This *ester* was prepared in the same manner as the sarcosine derivative. Recrystallised from ethyl acetate–light petroleum (b. p. 40—60°), it had m. p. 123—124° (Found: C, 51·9; H, 4·9; N, 7·2; P, 8·4; S, 8·2. $C_{17}H_{19}O_5N_2SP$ requires C, 51·8; H, 4·9; N, 7·1; P, 7·9; S, 8·1%). It was also obtained by keeping a solution of methyl *N*-diphenoxyphosphinyldithiocarbamate (0·75 g.) and glycine ethyl ester (0·25 g.) in ethanol (5 c.c.) overnight. Evaporation of the solvent under reduced pressure gave an oil which crystallised at 0°. Recrystallisation from ethyl acetate–light petroleum (b. p. 40—60°) and then from aqueous ethanol gave a product (0·5 g.), which had m. p. and mixed m. p. 124—125°. The two specimens had identical infrared spectra. This compound (0·3 g.) was heated in 4N-hydrochloric acid (15 c.c.) and ethanol (15 c.c.) for 3·5 hr. After concentration under reduced pressure to 10 c.c. the pH was adjusted to 7·5, and the solution was extracted continuously with ether overnight. Removal of ether afforded 2-thiohydantoin (15 mg.), which was recrystallised from water. It then had m. p. and mixed m. p. 224—226° (decomp.), and was indistinguishable from an authentic specimen on a paper chromatogram irrigated with butan-1-ol saturated with water.

Reaction of diphenyl phosphoroisothiocyanatidate or methyl *N*-diphenoxyphosphinyldithiocarbamate and glycylglycine ethyl ester gave intractable gums. Treatment of these with 90% trifluoroacetic acid or a mixture of water (1 vol.) and acetic acid saturated with hydrogen chloride (9 vols.) gave only traces of 2-thiohydantoin detectable by paper chromatography.

Diethyl Phosphoroisothiocyanatidate (I; R = Et).—This compound was prepared by the methods of Kenner *et al.*[8] (54%) and Michalski and Wieczorkowski[6] (74%) and had b. p. 70—72°/0·6 mm., n_D^{19} 1·4751 (Found: C, 30·8; H, 5·1; N, 7·1; P, 15·1. Calc. for $C_5H_{10}O_3NSP$: C, 30·8; H, 5·2; N, 7·2; P, 15·9%). There was a broad band at 1980—2050 cm.$^{-1}$ with a shoulder at *ca.* 2070 cm.$^{-1}$ in the infrared spectrum.

N-*Diethoxyphosphinyl*-N′-*ethylthiourea* (II; R = R′ = Et, R″ = H).—Reaction between equimolar quantities of diethyl phosphoroisothiocyanatidate and ethylamine in benzene or acetonitrile afforded this *thiourea* (0—31%), which crystallised from benzene–light petroleum (b. p. 40—60°). Recrystallised from carbon tetrachloride–light petroleum (b. p. 40—60°), it had m. p. 61—62° (Found: C, 34·9; H, 7·1; N, 11·6; P, 13·1; S, 13·7. $C_7H_{17}O_3N_2SP$ requires C, 35·0; H, 7·1; N, 11·7; P, 12·9; S, 13·4%).

N-*Cyclohexyl*-N′-*diethoxyphosphinylthiourea* (II; R = Et, R′ = C_6H_{11}, R″ = H).—This *compound* (34—61%), prepared in a similar manner, crystallised from benzene–light petroleum (b. p. 40—60°). After recrystallisation from light petroleum (b. p. 60—80°), it had m. p. 91—92° (Found: C, 45·0; H, 7·8; P, 10·7. $C_{11}H_{23}O_3N_2SP$ requires C, 44·9; H, 7·9; P, 10·5%).

N-*Diethoxyphosphinyl*-N′-*t-butylthiourea* (II; R = Et, R′ = Bu^t, R″ = H).—Similarly prepared to the above compounds, this *thiourea* (15—24%) crystallised from light petroleum (b. p. 90—120°) and had m. p. 108—109° (Found: C, 40·4; H, 7·9; N, 10·4; P, 12·3; S, 12·4. $C_9H_{21}O_3N_2SP$ requires C, 40·3; H, 7·9; N, 10·4; P, 11·6; S, 12·0%).

Dibenzyl Phosphoroisothiocyanatidate (I; R = Ph·CH_2).—A solution of thiocyanogen (0·1 mole) in carbon tetrachloride (250 c.c.) was added during 4 hr. to a well-stirred solution of dibenzyl phosphite (0·075 mole) in carbon tetrachloride (200 c.c.) at a temperature below −10°.

[17] Elmore, unpublished work.

The mixture was kept at 0° for 48 hr., filtered through Hyflo-Supercel, and aerated with a brisk stream of nitrogen for 1 hr. This solution was used without further purification for the experiments described below. Use of 0·4 mole of thiocyanogen or increase of the time of reaction to 96 hr. did not improve yields in the subsequent reactions.

N-*Dibenzyloxyphosphinyl*-N′-*phenylthiourea* (II; R = Ph·CH_2, R′ = Ph, R″ = H).—Aniline (2·8 g.), added to an aliquot part (90 c.c.) of the solution of dibenzyl phosphoroisothiocyanatidate prepared as described above, caused a yellow oil to separate immediately. After 3 hr., chloroform (90 c.c.) was added, and the mixture was successively extracted with 2N-hydrochloric acid, saturated sodium hydrogen carbonate and water (twice), and dried (Na_2SO_4). Concentration under reduced pressure to 25 c.c. and addition of light petroleum (b. p. 40—60°) caused the *thiourea* (1·35 g.) to separate. Recrystallised from ethyl acetate–light petroleum (b. p. 40—60°), it had m. p. 107—108° (Found: C, 60·7; H, 5·2; N, 6·9; P, 7·6; S, 8·1. $C_{21}H_{21}O_3N_2SP$ requires C, 61·2; H, 5·1; N, 6·8; P, 7·5; S, 7·8%). Two subsequent experiments gave yields of 0·66 g. and 1·90 g.

O-*Benzyl*-N-*phenylthiocarbamoylphosphoramidic Acid.*—The sodium hydrogen carbonate extract obtained in the foregoing experiment was strongly acidified and extracted with 6 portions of ether. To the combined and dried (Na_2SO_4) ether extracts was added an excess of cyclohexylamine. The resultant *cyclohexylammonium* O-*benzyl*-N-*phenylthiocarbamoylphosphoramidate* (VII; R = C_6H_{11}) (1·2 g.) was recrystallised first from 95% ethanol and then from 10% ethanol, and had m. p. 151—152° (Found: C, 56·7; H, 6·4; N, 9·8; P, 7·8; S, 8·0. $C_{20}H_{28}O_3N_3SP$ requires C, 57·0; H, 6·7; N, 10·0; P, 7·4; S, 7·6%).

Aniline (5·8 g.) was added to an aliquot part (90 c.c.) of the isothiocyanatidate solution described above, and the mixture was kept overnight at room temperature. The oil (2·65 g.), which initially separated, solidified to a gummy solid and was collected and washed with chloroform. Dissolution in hot chloroform and addition of light petroleum (b. p. 40—60°) afforded *anilinium* O-*benzyl* N-*phenylthiocarbamoylphosphoramidate* (VII; R = Ph) (1·5 g.). After recrystallisation first from ethanol–ether–light petroleum (b. p. 40—60°) and then from ethanol–cyclohexane, it had m. p. 138—140° (Found: C, 58·1; H, 5·2; N, 9·8; P, 7·8; S, 8·0. $C_{20}H_{22}O_3N_3SP$ requires C, 57·8; H, 5·3; N, 10·1; P, 7·5; S, 7·7%). It was found impossible to isolate *N*-dibenzyloxyphosphinyl-*N′*-phenylthiourea from the carbon tetrachloride mother-liquors from this preparation.

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