References and Notes

(1) P. J. Garratt and D. N. Nicolaides, *Chem. Commun.*, 1014 (1972).
(2) S. W. Longworth and J. F. W. McOmie, *Chem. Commun.*, 623 (1972).
(3) P. J. Garratt and K. P. C. Vollhardt, *J. Amer. Chem. Soc.*, **94**, 1023 (1972). The related tricyclic compound 2-thianorbiphenylene has also been synthesized: P. J. Garratt and K. P. C. Vollhardt, *ibid.*, **94**, 7087 (1972).
(4) M. P. Cava, R. H. Schlessinger, and J. P. Van Meter, *J. Amer. Chem. Soc.*, **86**, 3173 (1964).
(5) M. P. Cava, M. Behforouz, G. E. M. Husbands, and M. Srinivasan, *J. Amer. Chem. Soc.*, **95**, 2561 (1973).
(6) L. A. Carpino, *J. Amer. Chem. Soc.*, **84**, 2196 (1962).
(7) D. W. H. MacDowell and J. C. Wisowaty, *J. Org. Chem.*, **36**, 3999 (1971).
(8) M. V. Lakshmikantham, unpublished observations.
(9) M. P. Cava, B. Hwang, and J. P. Van Meter, *J. Amer. Chem. Soc.*, **85**, 4051 (1963).
(10) M. P. Cava and D. Mangold, *Tetrahedron Lett.*, 1751 (1964).
(11) F. R. Jensen and W. E. Colman, *J. Amer. Chem. Soc.*, **80**, 6149 (1958).
(12) J. M. McGrady, unpublished observations.
(13) For examples of some condensed thiophenes having considerable tetracovalent sulfur character see ref 5 and (a) M. P. Cava and M. A. Sprecker, *J. Amer. Chem. Soc.*, **94**, 6214 (1972); (b) K. T. Potts and D. McKeough, *ibid.*, **94**, 6215 (1972); (c) K. T. Potts and D. McKeough, *ibid.*, **95**, 2750 (1973).
(14) R. B. Woodward and R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **8**, 781 (1969).
(15) M. P. Cava and D. R. Napier, *J. Amer. Chem. Soc.*, **80**, 2255 (1958).
(16) M. P. Cava and R. L. Shirley, *J. Amer. Chem. Soc.*, **82**, 654 (1960).

Urylenediphosphonates. A General Method for the Synthesis of α-Ureidophosphonates and Related Structures

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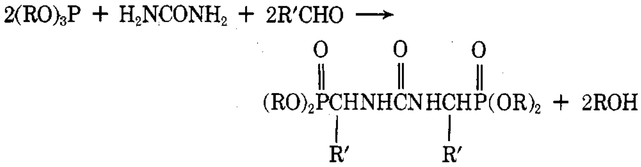
Urea and many mono- and disubstituted ureas and their thio analogs react with aldehydes and certain esters of trivalent phosphorus acids, providing a route to numerous new α-ureidophosphonates, $(RO)_2P(O)CHR'NHCONH_2$, and related products. Surprisingly, triphenyl phosphite is more readily converted to phosphonates in this process than are trialkyl phosphites, a reversal of the normal order of reactivity of phosphite esters. Acid catalysis is beneficial in some cases. Urylenediphosphonates, $(RO)_2P(O)CHR'NHCONHCHR'P(O)(OR)_2$, as well as monophosphonates are obtained when unsubstituted urea is used, whereas mono- and disubstituted ureas give only monophosphonates. Phosphonite and phosphinite esters react similarly, giving ureaphosphinates and -phosphine oxides, respectively. Cyclic 1,4,2-diazaphospholidins are the major products when 1,3-dimethylurea is used. Many of the products can be readily hydrolyzed to the corresponding ureidophosphonic and -phosphinic acids.

While the synthesis and properties of many types of nitrogen-containing organophosphorus compounds have been widely investigated,[1] for example, aminophosphonates in biochemical[2] and in chelation[3,4] studies, ureaphosphonates have received little attention. In connection with our interests in new biologically active structures and in permanent fire retardancy of polymers,[5] a search was made for routes to urea derivatives having organophosphorus substituents. The resulting investigation led to the discovery that urea and many mono- and disubstituted ureas and their thio analogs will react with certain esters of trivalent phosphorus acids and aldehydes to give α-ureidophosphonates and related products. Numerous compounds can be synthesized by this process, since the structures of all three reactants are subject to broad variation.

The application of this new reaction to the preparation of urylenediphosphonates (**1a–d**) from urea, phosphite esters, and aldehydes is represented by the following equation.

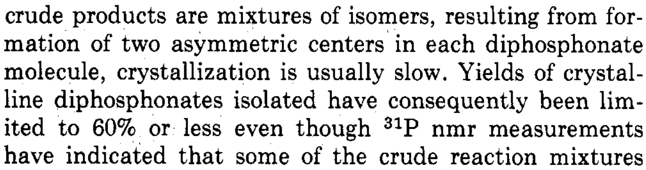


$$2(RO)_3P + H_2NCONH_2 + 2R'CHO \longrightarrow (RO)_2\overset{O}{\overset{\|}{P}}\underset{R'}{CH}NH\overset{O}{\overset{\|}{C}}NH\underset{R'}{CH}\overset{O}{\overset{\|}{P}}(OR)_2 + 2ROH$$

1a, $R = C_6H_5$; $R' = CH_3$
b, $R = C_6H_5$; $R' = C_6H_5$
c, $R = CH_2CH_2Cl$; $R' = CH_3$
d, $R = CH_2CH_2Cl$; $R' = CH(CH_3)_2$

Generally, the reaction is initiated when a mixture of the three reactants is warmed to about 60–70°; it is usually complete after 10–15 min at 70–100°. Alternatively, the aldehyde may be added gradually to a mixture of urea and the phosphite ester at this temperature. Since the crude products are mixtures of isomers, resulting from formation of two asymmetric centers in each diphosphonate molecule, crystallization is usually slow. Yields of crystalline diphosphonates isolated have consequently been limited to 60% or less even though ^{31}P nmr measurements have indicated that some of the crude reaction mixtures contained considerably more material.

Although thiourea is less reactive than urea in this process, results are satisfactory when it is used with triphenyl phosphite and an alkyl aldehyde. Tetraphenyl (thiourylenedibutyl)diphosphonate (**2**) was obtained from thiourea, triphenyl phosphite and *n*-butyraldehyde in nearly a quantitative yield according to ^{31}P nmr measurements.

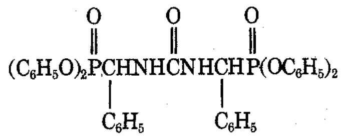


$$2(C_6H_5O)_3P + H_2NCSNH_2 + 2CH_3CH_2CH_2CHO \longrightarrow (C_6H_5O)_2\overset{O}{\overset{\|}{P}}\underset{CH_3CH_2CH_2}{CH}NH\overset{S}{\overset{\|}{C}}NH\underset{CH_2CH_2CH_3}{CH}\overset{O}{\overset{\|}{P}}(OC_6H_5)_2 + 2C_6H_5OH$$

2

In a few cases two fractions, presumably *dl* and meso forms, were isolated. Tetraphenyl (urylenedibenzyl)diphosphonate (**1b**), for example, was separated into fractions I and II.

The observed ^{31}P and ^{1}H nmr multiplets for I and II were consistent with the expected phosphorus–hydrogen and hydrogen–hydrogen spin couplings for structure **1b**. Conversion of the ^{1}H nmr doublet of doublets for each fraction to a simple doublet, $J_{CHNH} = 10$ Hz, by heteronuclear ^{31}P spin decoupling provided further evidence of the



$$(C_6H_5O)_2\overset{\overset{O}{\|}}{P}\underset{\underset{C_6H_5}{|}}{C}HNH\overset{\overset{O}{\|}}{C}NH\underset{\underset{C_6H_5}{|}}{C}H\overset{\overset{O}{\|}}{P}(OC_6H_5)_2$$

1b

Fraction I

Mp 189-191 °C
$\delta^{31}P$ −14.7 (d, J_{PCH} = 22 Hz)
$\delta^{1}H$ 5.98 (d of d, J_{CHP} = 22 Hz, J_{CHNH} = 10 Hz)
Ir 5.88 (C═O), 8.38 μ (P═O)

Fraction II

Mp 181-183 °C
$\delta^{31}P$ −15.5 (d, J_{PCH} = 22 Hz)
$\delta^{1}H$ 6.06 (d of d, J_{CHP} = 22 Hz, J_{CHNH} = 10 Hz)
Ir 5.88 (C═O), 8.38 μ (P═O)

presence of the PCHNH moiety. Infrared spectra, elemental analyses, and molecular weight measurements (see Experimental Section) also were in agreement with **1b**. A sharply depressed mixture melting point for I and II, as well as small but real nmr chemical shift differences, confirmed that these fractions were isomers.

Surprisingly, triaryl phosphites are markedly more reactive in this process than are trialkyl phosphites. For example, when a mixture of triphenyl phosphite, *n*-butyraldehyde, and urea (2:2:1 molar ratio) in toluene was warmed, reaction was initiated at 70°, and cooling was needed for several minutes to keep the temperature below 90° as the urea dissolved. The reaction was complete in less than 0.5 hr according to ^{31}P nmr. When triethyl phosphite was used under similar conditions, the urea did not dissolve, and there was no indication of reaction after 1 hr at 95-100°. Trimethyl and triisopropyl phosphites were similarly unreactive. Tris(2-chloroalkyl) phosphites, normally intermediate in reactivity in the phosphite series, reacted readily when alkyl aldehydes were used but only slowly with less reactive aryl aldehydes.

This may be the first known reaction in which triaryl phosphites are more readily converted to phosphonates than are low molecular weight trialkyl phosphites. The literature reports the synthesis of hundreds of phosphonates from the normally reactive trialkyl phosphites by the Michaelis-Arbuzov reaction and some of its variations[6-10] but gives comparatively few examples of phosphonates being prepared from triaryl phosphites. Triaryl phosphites usually form relatively stable intermediates that require drastic heating or treatment with aqueous alkali or alcohols for conversion to phosphonates.[6-10] It is thus unexpected that aryl phosphites should be converted to phosphonates under mild conditions in the present reaction whereas alkyl phosphites are unreactive under the same conditions.

Experimental observations that may explain this reversal of the normal order of reactivity of phosphite esters are listed below.

(1) Urea and *n*-butyraldehyde reacted readily and formed a polymer when a mixture was warmed to ~60°.

(2) Reaction of urea with *n*-butyraldehyde was inhibited when triethylamine was present.

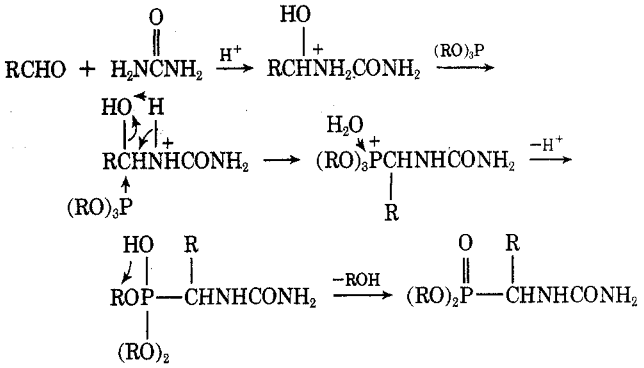
(3) Reaction of urea and *n*-butyraldehyde was also inhibited by triethyl phosphite.

(4) Reaction of triphenyl phosphite with urea and *n*-butyraldehyde was inhibited when triethyl phosphite was present.

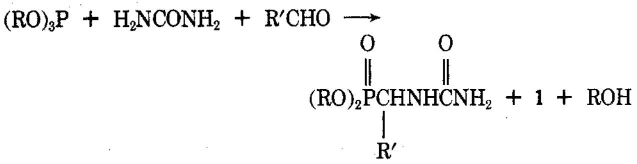
(5) The addition of acetic acid or boron trifluoride etherate to mixtures of triethyl phosphite, urea, and *n*-butyraldehyde or benzaldehyde promoted the formation of ureaphosphonates.

Evidently, the first step in the formation of ureaphosphonates is an acid-catalyzed reaction of urea and aldehyde as shown in Scheme I. Trialkyl phosphites, such as triethyl phosphite, are basic enough to inhibit this first step, whereas the less basic triphenyl phosphite[11] does not lower the acidity below the level needed for reaction of urea and aldehyde. Tris(2-chloroalkyl) phosphites, which are intermediate in nucleophilicity and probably in basicity,[12] are less reactive than triaryl phosphites but more reactive than unsubstituted trialkyl phosphites.

Scheme I

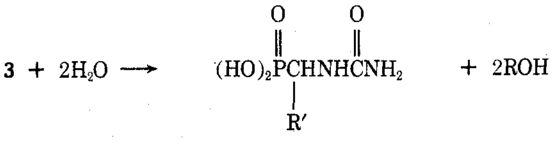


Since the formation of urea monophosphonates, such as **3a** and **3b**, is accompanied by formation of diphosphonates even when equimolar quantities of reactants are used, pure monophosphonates are usually difficult to isolate. Fortunately, the monophosphonates hydrolyze more readily than the diphosphonates, and the resulting phosphonic acids can be easily isolated. Pure ureaphosphonic acids **4a** and **4b** were obtained after crude mixtures of the phosphonates were warmed with distilled water. Presumably, the unsubstituted NH_2 group, in a position that can allow formation of a five-membered ring with phosphorus, participates in the hydrolysis of the monophosphonates. The ureadiphosphonic acid **5a** was obtained only after **1d** was warmed with dilute hydrochloric acid for several hours.



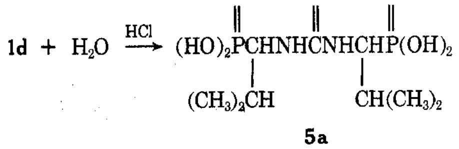
$$(RO)_3P + H_2NCONH_2 + R'CHO \longrightarrow (RO)_2\overset{\overset{O}{\|}}{P}\underset{\underset{R'}{|}}{C}HNH\overset{\overset{O}{\|}}{C}NH_2 + \mathbf{1} + ROH$$

3a, R = CH_2CH_2Cl; R′ = CH_2CH_3
b, R = CH_2CH_2Cl; R′ = $CH(C_2H_5)(CH_2)_3CH_3$



$$\mathbf{3} + 2H_2O \longrightarrow (HO)_2\overset{\overset{O}{\|}}{P}\underset{\underset{R'}{|}}{C}HNH\overset{\overset{O}{\|}}{C}NH_2 + 2ROH$$

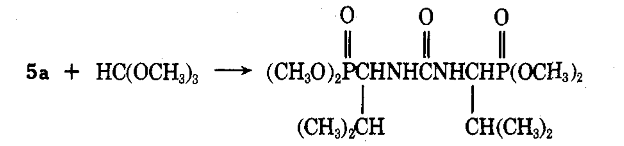
4a, R′ = CH_2CH_3
b, R′ = $CH(C_2H_5)(CH_2)_3CH_3$



$$\mathbf{1d} + H_2O \xrightarrow{HCl} (HO)_2\overset{\overset{O}{\|}}{P}\underset{\underset{(CH_3)_2CH}{|}}{C}HNH\overset{\overset{O}{\|}}{C}NH\underset{\underset{CH(CH_3)_2}{|}}{C}H\overset{\overset{O}{\|}}{P}(OH)_2$$

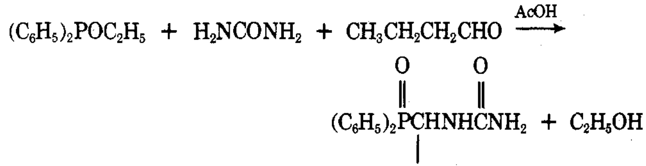
5a

The tetramethyl ester of **5a** was synthesized by esterification of the acid with trimethyl orthoformate.


$$\mathbf{5a} + HC(OCH_3)_3 \longrightarrow (CH_3O)_2\overset{\overset{O}{\|}}{P}\underset{\underset{(CH_3)_2CH}{|}}{C}HNH\overset{\overset{O}{\|}}{C}NH\underset{\underset{CH(CH_3)_2}{|}}{C}H\overset{\overset{O}{\|}}{P}(OCH_3)_2$$

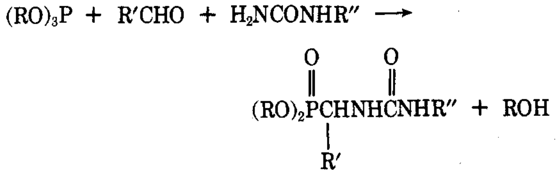
5b

Aryl and 2-chloroalkyl esters of phenylphosphonous and diphenylphosphinous acids also react readily with urea and aldehydes. The alkyl ester, ethyl diphenylphosphinite, required the addition of an acid for reaction with urea and *n*-butyraldehyde. The monosubstituted product, diphenyl(1-ureidobutyl)phosphine oxide (**6**), was isolated in this case.

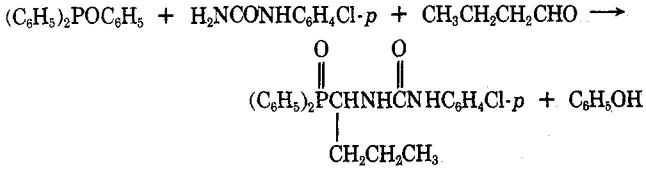

$$(C_6H_5)_2POC_2H_5 + H_2NCONH_2 + CH_3CH_2CH_2CHO \xrightarrow{AcOH} (C_6H_5)_2\overset{\overset{O}{\|}}{P}\underset{\underset{CH_2CH_2CH_3}{|}}{C}HNH\overset{\overset{O}{\|}}{C}NH_2 + C_2H_5OH$$

6

Ureidophosphonates **7a–c** were prepared from monosubstituted ureas. Acid catalysis again was needed for the formation of **7c** from triethyl phosphite. *p*-Chlorophenylurea, phenyl diphenylphosphinite, and *n*-butyraldehyde gave phosphine oxide **8**.

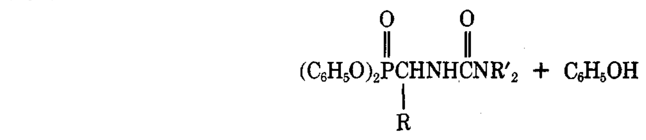

$$(RO)_3P + R'CHO + H_2NCONHR'' \longrightarrow (RO)_2\overset{\overset{O}{\|}}{P}\underset{\underset{R'}{|}}{C}HNH\overset{\overset{O}{\|}}{C}NHR'' + ROH$$

7a, R = C_6H_5; R' = $CH_2CH_2CH_3$; R'' = $CH_2CO_2C_2H_5$
b, R = C_6H_5; R' = 3-$CH_3OC_6H_3OH$-4; R'' = 4-ClC_6H_4
c, R = C_2H_5; R' = C_6H_5; R'' = C_6H_5

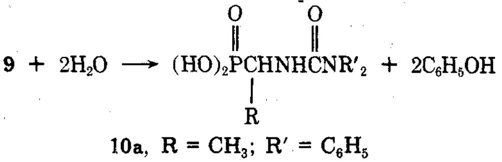

$$(C_6H_5)_2POC_6H_5 + H_2NCONHC_6H_4Cl\text{-}p + CH_3CH_2CH_2CHO \longrightarrow (C_6H_5)_2\overset{\overset{O}{\|}}{P}\underset{\underset{CH_2CH_2CH_3}{|}}{C}HNH\overset{\overset{O}{\|}}{C}NHC_6H_4Cl\text{-}p + C_6H_5OH$$

8

Similarly, ureidophosphonates **9a** and **9b** were prepared from 1,1-disubstituted ureas, and the esters were hydrolyzed to phosphonic acids **10a** and **10b**.

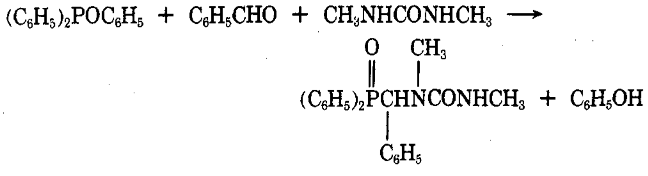

$$(C_6H_5O)_3P + RCHO + H_2NCONR'_2 \longrightarrow (C_6H_5O)_2\overset{\overset{O}{\|}}{P}\underset{\underset{R}{|}}{C}HNH\overset{\overset{O}{\|}}{C}NR'_2 + C_6H_5OH$$

9a, R = CH_3; R' = C_6H_5
b, R = $C_6H_4NO_2$-4; R' = CH_3


$$\mathbf{9} + 2H_2O \longrightarrow (HO)_2\overset{\overset{O}{\|}}{P}\underset{\underset{R}{|}}{C}HNH\overset{\overset{O}{\|}}{C}NR'_2 + 2C_6H_5OH$$

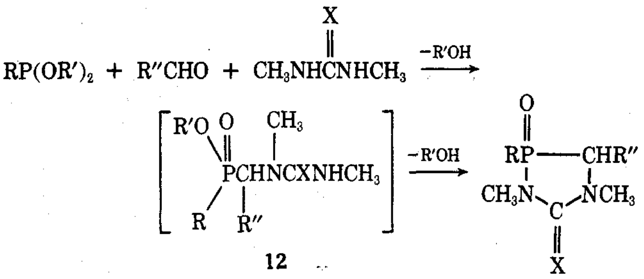
10a, R = CH_3; R' = C_6H_5
b, R = $C_6H_4NO_2$-4; R' = CH_3

1,3-Dimethylurea gave two types of products, depending on the kind of phosphorus ester that was used. With phenyl diphenylphosphinite and benzaldehyde, a normal reaction occurred, and phosphine oxide **11** was obtained.


$$(C_6H_5)_2POC_6H_5 + C_6H_5CHO + CH_3NHCONHCH_3 \longrightarrow (C_6H_5)_2\overset{\overset{O}{\|}}{P}\underset{\underset{C_6H_5}{|}}{C}H\overset{\overset{CH_3}{|}}{N}CONHCH_3 + C_6H_5OH$$

11

However, when phosphite and phosphonite esters were used with 1,3-dimethylurea or its thio analog, cyclic 1,4,2-diazophospholidins (**13**) were the major products instead of linear structures such as those obtained in the preceding cases.



12 **13**

Some sulfamides, sulfonamides, and carbamates have also been found to react similarly to ureas with aldehydes and esters of trivalent phosphorus acids to give isolable crystalline products. Details of these results will be reported later. Moderate success with acid catalysis in several cases suggests that the process can probably be broadened in applicability by further study.

Experimental Section

Melting points were obtained in a Thomas-Hoover Unimelt instrument. Infrared spectra were determined in potassium bromide disks on a Beckman IR-4 spectrophotometer. Proton nuclear magnetic resonance (nmr) spectra were obtained at 60.0 or 100.0 MHz on Varian I-60 or HR-100 spectrometers with tetramethylsilane as an internal standard. Phosphorus nmr spectra were determined at 24.3 or 40.5 MHz on Varian HR-60 or HR-100 instruments and are reported with respect to 85% H_3PO_4 contained in a capillary. The nmr measurements were generally made on saturated solutions. Mass spectra were obtained on a Consolidated Engineering Corp. Type 21-104 spectrometer fitted with a probe for direct introduction of solids. Acid dissociation constants were determined from potentiometric titration data using the pH values at the midpoints of the titration curves.[13] Elemental analyses and molecular weights were determined by Galbraith Laboratories, Knoxville, Tenn.

Tetraphenyl (Urylenediethyl)diphosphonate (1a). A mixture of 60.0 g (1.0 mol) of powdered urea, 620.5 g (2.0 mol) of freshly distilled triphenyl phosphite, and 88.0 g (2.0 mol) of freshly distilled acetaldehyde in 600 g of 1,2-dichloroethane was stirred under nitrogen and warmed to 60° to initiate reaction. Cooling was used for a few minutes to keep the temperature below 80°, and the reaction mixture was then warmed at 80–84° for 0.5 hr to give a light tan solution having ^{31}P nmr signals at −19.7 (m) and −16.1 ppm (trace). The solution was washed three times with 10% sodium carbonate solution and three times with water, and it was then stripped to 130° (0.3 mm) to give 508.5 g (87.6%) of yellow, viscous oil having a ^{31}P nmr signal only at −19.9 ppm. A solution of 158 g of this oil in acetonitrile was refrigerated for 3 days to induce crystallization. It was then filtered, and the solid was washed with acetonitrile, giving 112.3 g (62%) of white solid, mp ∼125–155°. Repeated recrystallizations from acetonitrile gave fractions I and II. Fraction I had mp 136–138°; ^{31}P nmr ($CDCl_3$) −19.7 ppm (m, $J \cong 18$ Hz); ^1H nmr δ 7.21 (m, 20, C_6H_5), 6.46 (d, 2, J = 12 Hz, NH, collapsed to a singlet upon homonuclear decoupling), 4.86 (m, 2, CH), 1.30 (d of d, 6, J = 18 and 7.5 Hz, CH_3, collapsed to a doublet, J = 7.5 Hz, upon irradiation with 40.5 MHz at 750 Hz and to a doublet, J = 18 Hz, upon homonuclear decoupling): ir (KBr) 2.99 (m), 3.27 (w), 5.92 (s), 6.26 (m), 6.43 (s), 6.68 (s), 8.40 (vs), 10.6 μ (vs); mol wt ($CHCl_3$) 572 (theory 580).

Anal. Calcd for $C_{29}H_{30}N_2O_7P_2$: C, 59.98; H, 5.21; N, 4.82; P, 10.67. Found: C, 60.08; H, 5.05; N, 4.67; P, 10.71.

Fraction II had mp 156–161°; ^{31}P nmr −20.5 ppm (m, $J \cong 17.8$ Hz); ^1H nmr δ 7.20 (m, 20), 6.55 (d, 2, J = 10 Hz, NH), 4.86 (m, 2, CH), 1.37 (d of d, 6, J = 18 and 7.5 Hz, CH_3); ir essentially identical with that of I.

When the reaction was repeated without the use of a solvent, the results were essentially the same according to nmr measurements. In this run the by-product phenol (81%) of theory) was removed from **1a** by stripping to 120° (1 mm).

Tetraphenyl (Urylenedibenzyl)diphosphonate (1b). A mixture of 60.0 g (1.0 mol) of powdered urea, 620.5 g (2.0 mol) of freshly distilled triphenyl phosphite, and 212.2 g (2.0 mol) of benzaldehyde in 600 g of 1,2-dichloroethane was stirred under nitrogen and warmed. The heating mantle was removed at 70°, and a cooling bath was used as needed for 0.3 hr to keep the temperature below 83°. The reaction mixture was warmed at reflux (93°) for 0.7 hr and then allowed to cool. One pint of CCl_4 was added and the solution was washed once with 1 l. of 10% NaOH solution, three times with 500 ml of 5% NaOH solution, and three times with 500 ml of water. Stripping to 115° (0.2 mm) gave 498 g (71%) of pale yellow viscous oil: ^{31}P nmr −15 ppm (overlapping doublets). Two fractions, I and II, were separated by repeated recrystallizations from acetone and acetonitrile. Fraction I was a white solid: mp 189–191°; ^{31}P nmr ($CDCl_3$) −14.7 ppm (d, J = 22 Hz); ^1H nmr δ 6.66–7.66 (m, 32, aryl and NH), 5.98 (d of d, 2, J = 22, 10 Hz, CH, collapsed to doublet, J = 10 Hz, when decoupled from phosphorus); ir (KBr) 2.98 (m), 3.27 (w), 5.88 (s), 6.27 (m), 6.43 (s), 6.67 (s), 8.38 (vs), 10.6 μ (vs); mol wt (acetone) 731 (theory 704).

Anal. Calcd for $C_{39}H_{34}N_2O_7P_2$: C, 66.47; H, 4.86; N, 3.98; P, 8.79. Found: C, 66.35; H, 4.82; N, 3.99; P, 9.08.

Fraction II was a white solid: mp 181–183°; ^{31}P nmr −15.5 ppm (d, J = 22 Hz); ^1H nmr δ 6.66–7.75 (m, 32, aryl and NH), 6.06 (d of d, 2, J = 22, 10 Hz, CH, collapsed to doublet, J = 10 Hz, when decoupled from phosphorus); ir (KBr) essentially the same as that of I; mol wt (acetone) 692 (theory 704).

Anal. Found: C, 66.45; H, 4.83; N, 3.93; P, 8.71. The mixture melting point of I and II was 159–173°.

Tetrakis(2-chloroethyl) (Urylenediethyl)diphosphonate (1c). A 2-l., four-necked flask equipped with a thermometer, mechanical stirrer, dropping funnel, and Dry Ice cooled condenser was swept with nitrogen and charged with 539.0 g (2.0 mol) of crude tris(2-chloroethyl) phosphite, 60.0 g (1.0 mol) of powdered urea, and one half of 94.6 g (2.15 mol) of freshly distilled acetaldehyde. When this mixture was warmed, refluxing began at 47° and the temperature gradually increased to 60° in 25 min. The mantle was removed, and heat of reaction raised the temperature to 82° in 15 min. The remainder of the acetaldehyde was then added below the surface of the reaction mixture in 11 min at 65–75°. Warming at 90–95° for 0.5 hr gave a clear, colorless solution, ^{31}P nmr −27.6 ppm. One pint of 1,2-dichloroethane was added, and the solution was washed five times with 400-ml portions of water and then stripped to 110° (0.2 mm) to give 469 g (89%) of colorless, viscous liquid: $n^{25}D$ 1.4991; ^{31}P nmr −27.8 ppm; mol wt (acetone) 520 (calcd 526).

Anal. Calcd for $C_{13}H_{26}Cl_4N_2O_7P_2$: C, 29.67; H, 4.98; Cl, 26.95; N, 5.32; P, 11.77. Found: C, 29.75; H, 5.08; Cl, 27.00; N, 5.22; P, 11.63.

A solid formed after a portion of the viscous liquid was several times diluted with acetone and finally with ether and the solvent was allowed to evaporate each time. Recrystallization twice from acetonitrile–ether gave a white solid: mp 138–140°; ^{31}P nmr −27.8 ppm (m); ^1H nmr δ 6.45 (d, 2, J = 10 Hz, NH), 4.1–4.8 (m, 10, $POCH_2$ and PCH), 3.5–3.9 (m, 8, $ClCH_2$), 1.38 (d of d, 6, J = 17 and 7 Hz, CH_3); ir (KBr) 2.97 (m), 3.33 (w), 5.89 (s), 6.38 (s), 6.83 (m), 7.93 (s), 8.13 (s), 9.65 μ (vs); mol wt (DMF) 516.

Anal. Found: C, 29.97; H, 5.09; Cl, 26.99; N, 5.28; P, 11.71.

Tetraphenyl (Thiourylenedibutyl)diphosphonate (2). When a mixture of 11.4 g (0.15 mol) of thiourea, 93.0 g (0.30 mol) of triphenyl phosphite, and 22.7 g (0.32 mol) of *n*-butyraldehyde in 74 g of toluene was warmed to 100°, reaction was initiated, and the temperature increased to 105° within a few minutes without external warming. The reaction mixture was then warmed at 105–110° for 1 hr to give a light yellow solution having a ^{31}P nmr peak at −18.0 ppm, the only observable signal. Concentration to 120° (0.5 mm) to remove solvent and most of the by-product phenol gave 103.5 g (theory 97.5 g) of viscous liquid that completely solidified on standing. Recrystallization of a portion twice from acetone and once from acetonitrile gave a white solid (**2**): mp 138–143°; ^{31}P nmr −18.1 ppm; ^1H nmr δ 7.3 (d, 2, J = 10 Hz, NH), 7.1 (m, 20, aryl), 5.8 (m, 2, CH), 0.3–2.1 (m, 14, $CH_2CH_2CH_3$); ir 3.04 (w), 3.26 (w), 3.40 (w), 6.28 (m), 6.45 (m), 6.70 (m), 7.36 (m), 7.93 (m), 8.29 (m), 8.43 (s), 10.6–10.7 (vs), 13.0 (vs), 14.5 μ (s); mol wt (acetone) 630 (calcd 652).

Anal. Calcd for $C_{33}H_{38}N_2O_6P_2S$: C, 60.72; H, 5.87; N, 4.29; P, 9.49; S, 4.91. Found: C, 60.87; H, 6.09; N, 4.55; P, 9.56; S, 5.08.

1-Ureidopropylphosphonic Acid (4a). Freshly distilled propionaldehyde (58.0 g, 1.0 mol) was added dropwise in 1 hr to a stirred mixture of 60.0 g (1.0 mol) of powdered urea and 269.5 g (1.0 mol) of crude tris(2-chloroethyl) phosphite at 105–112°. Heat of reaction kept the temperature at this level without external warming during most of the aldehyde addition. The reaction mixture was warmed for 0.25 hr more, and then it was stripped to 122° (2 mm), giving a viscous, yellow residue (crude **3a**). This was dissolved in 100 ml of acetonitrile and 36 g (2.0 mol) of water, and the solution was warmed at reflux for 1 hr. A solid that formed during warming was separated by filtration of the warm reaction mixture, and then it was stirred and warmed in more acetonitrile and water, and the mixture was filtered while warm to give 76.2 g (42%) of white solid, mp 185–186° dec. A 5.0-g portion was recrystallized from acetic acid–water to give 3.2 g of **4a**: mp 189–191° dec; ^{31}P nmr (CD_3SOCD_3) −23.0 ppm (m); ^1H nmr δ 8.5 (broad, 4, OH and NH_2), 6.2 (broad, 1, NH), 3.7 (broad, 1, CH), 1.6 and 0.9 (broad, 5, CH_2CH_3); acidity 2.01 equiv/mol, pK_1 = 2.70, pK_2 = 7.30.

Anal. Calcd for $C_4H_{11}N_2O_4P$: C, 26.38; H, 6.09; N, 15.38; P, 17.01. Found: C, 26.50; H, 6.11; N, 15.26; P, 16.99.

2-Ethyl-1-ureidohexylphosphonic Acid (4b). This compound was prepared from tris(2-chloroethyl) phosphite, urea, and isobutyraldehyde by a procedure similar to that used for the preparathe preparation of 1-ureidopropylphosphonic acid. It was a white solid: mp 206° dec; ^{31}P nmr (CD_3SOCD_3) −23.2 ppm; ^1H nmr δ 8.5 (broad, 4, HO and NH_2), 6.2 (d, 1, J = 8 Hz, NH), 4.3 (d of d, 1, J = 8, 20 Hz, PCH), 1.3 and 0.9 (m, 15); acidity 2.00 equiv/mol, pK_1 = 3.50, pK_2 = 9.08.

Anal. Calcd for $C_9H_{21}O_4N_2P$: C, 42.85; H, 8.39; N, 11.11; P, 12.28. Found: C, 42.89; H, 8.29; N, 11.09; P, 12.23.

[Urylenedi(2-methylpropyl)]diphosphonic Acid (5a). Tetrakis(2-chloroethyl) [urylenedi(2-methylpropyl)]diphosphonate (**1d**) was prepared from tris(2-chloroethyl) phosphite, urea, and isobutyraldehyde by a procedure similar to that used for the preparation of **1c**. When a solution of 11.8 g (0.02 mol) of **1d**, mp 146–150°, and 2.9 g (0.16 mol) of distilled H_2O in 75 ml of acetonitrile was warmed at reflux for 7 hr, **1d** was recovered unchanged. The recovered **1d** was then stirred at reflux with 2.9 g of distilled H_2O and 1 ml of concentrated hydrochloric acid in 75 ml of acetonitrile for 6 hr. A solid, 4.4 g (67%), that separated during this warming period was recrystallized from $CH_3CN–H_2O$ and then from $CH_3CO_2H–H_2O$ to give white solid **5a** which appeared to melt at ~215°, resolidify, and then remelt at ~275–280° with foaming: ^{31}P nmr (DMSO-d_6) −22.8 ppm (m); ^1H nmr δ 8.6 (s, ~5, HO and NH?), 6.3 (broad, 1, NH), 3.8 (m, 2, CHP), 2.0 [m, 2, $CH(CH_3)_2$]; acidity by potentiometric titration 4.10 equiv/mol, pK_1 = 2.71, pK_2 = 8.24.

Anal. Calcd for $C_9H_{22}N_2O_7P_2$: C, 32.54; H, 6.68; N, 8.43; P, 18.64. Found: C, 32.64; H, 6.40; N, 8.35; P, 18.51.

Tetramethyl [Urylenedi(2-methylpropyl)]diphosphonate (5b). A mixture of 2.0 g of **5a** in 24 g of trimethyl orthoformate was warmed at reflux for 18 hr. Low boilers were removed by fractionation through a short column during the reflux period. The excess orthoformate was then distilled at reduced pressure, the residue was diluted with ether, and this mixture was filtered to give 0.5 g of solid. Recrystallization from acetone gave tetramethyl [urylenedi(2-methylpropyl)]diphosphonate (**5b**) as a white solid: mp 182–184.5°; ^{31}P nmr ($CDCl_3$) −27.7 ppm; ^1H nmr δ 6.61 (d, 2, J = 10 Hz, CHNH), 4.3 [four doublets, 2, J(CH-P) = 18, J(CH-NH) = 10, J(CH-CH) = 4 Hz, PCH(CH)NH], 3.76 [d, 6, $J(CH_3OP)$ = 10 Hz], 3.73 [d, 6, $J(CH_3OP)$ = 10 Hz], 2.06 [m, 2, $CH(CH_3)_2$], 1.03 [d, 12, J = 7 Hz, $CH(CH_3)_2$]; ir (KBr) 2.84 (w), 3.00 (m), 3.37 (m), 5.93 (s), 6.37 (s), 6.79 (m), 7.72 (m), 8.04 μ (vs).

Diphenyl(1-ureidobutyl)phosphine Oxide (6). After a mixture of 0.50 mol of ethyl diphenylphosphinite, 0.55 mol of *n*-butyraldehyde, and 0.25 mol of urea in 150 ml of chlorobenzene had been warmed at 110° for 3 hr, a ^{31}P nmr measurement showed a signal only for unreacted phosphite at −108.6 ppm. The mixture was cooled to room temperature and 0.25 mol of acetic acid was added dropwise in ~10 min. The temperature increased to 65° during this addition; the urea dissolved and then a white solid product separated. The addition of another 0.25 mol of acetic acid caused no additional heat of reaction. The reaction mixture was warmed at 65-80° for 1.5 hr and filtered, giving 44.4 g. Recrystallization from ethylene glycol gave 26.5 g of **6**, a white solid: mp 241-244°; ^{31}P nmr (CF_3CO_2H) −44.4 ppm; mass spectrum M^+ 316 (theory 316).

Anal. Calcd for $C_{17}H_{21}N_2O_2P$: N, 8.85; P, 9.79. Found: N, 8.62; P, 9.94.

Ethyl [3-(1-Diphenoxyphosphinylbutyl)ureido]acetate (7a). When a mixture of 43.8 g (0.3 mol) of ethyl hydantoate, 93.0 g (0.3 mol) of triphenyl phosphite, and 21.6 g (0.3 mol) of *n*-butyraldehyde in 100 g of benzene was warmed to 65°, heat of reaction became sufficient to raise the temperature to 82° (reflux) without external warming. Warming at reflux was continued for 0.5 hr, giving a clear, colorless solution having a single ^{31}P nmr peak, −19.2 ppm. The solvent and most of the phenol were removed by stripping to 117° (1 mm). The crude product was diluted with an equal volume of ether, and this solution was cooled to 10° and filtered to give 87.6 g (68%) of white solid (**7a**): mp 114-116° (from CH_3CN); ^{31}P nmr −19.7 ppm; ^{1}H nmr δ 7.1 (m, 10, aryl), 6.5 (d, 1, J = 10 Hz, CHNH), 6.1 (broad, 1, $NHCH_2$), 4.8 (m, 1, CH), 4.1 (q, 2, J = 7 Hz, OCH_2CH_3), 3.8 (broad, 2, $\mathbf{NHCH_2}$), 1.2 (t, 3, J = 7 Hz, OCH_2CH_3), 0.8-1.5 (m, 7, $CH_2CH_2CH_3$).

Anal. Calcd for $C_{21}H_{27}N_2O_6P$: C, 58.04; H, 6.26; N, 6.45; P, 7.13. Found: C, 57.82; H, 6.19: N, 6.24; P, 6.89.

Diphenyl α-[3-(4-Chlorophenyl)ureido]-4-hydroxy-3-methoxybenzylphosphonate (7b). A mixture of 34.1 g (0.2 mol) of 4-chlorophenylurea, 62.1 g (0.2 mol) of triphenyl phosphite, and 30.4 g (0.2 mol) of vanillin in 150 ml of benzene was warmed at reflux for 2.5 hr. The reaction mixture was cooled and filtered to give a light yellow solid which was twice recrystallized from acetonitrile-ethylene dichloride to give **7b**: mp 190-194° dec; ^{31}P nmr −15.8 ppm (d, J = 22 Hz); ^{1}H nmr δ 9.1 (s, 1, NHC_6H_4Cl), 8.7 (s, 1, OH), 6.7-7.8 (m, 18, aryl and CHNH), 5.7 (d of d, 1, J = 22, 10 Hz, PCHNH), 3.8 (s, 3, CH_3).

Anal. Calcd for $C_{27}H_{24}ClN_2O_6P$: C, 60.17; H, 4.48; Cl, 6.58; N, 5.19; P, 5.75. Found: C, 59.62; H, 4.36; Cl, 6.50; N, 5.13; P, 5.65.

Diethyl α-(3-Phenylureido)benzylphosphonate (7c). A ^{31}P nmr measurement indicated that there was no reaction when a mixture of 0.30 mol of triethyl phosphite, 0.30 mol of phenylurea, and 0.33 mol of benzaldehyde in 150 g of toluene was warmed at 95-100° for 0.5 hr. Boron trifluoride etherate (0.05 mol) was then added dropwise, causing a temperature rise. The reaction mixture was warmed at 95-100° for 1 hr and then stripped to a pot temperature of 120° (10 mm). The residue was diluted with ether, causing separation of a solid (75.7 g, including additional fractions from the filtrate). Recrystallization of a portion from acetonitrile gave a white solid: mp 150-151.5°; ^{31}P nmr ($CDCl_3$) −23.1 ppm; ^{1}H nmr δ 8.35 (s, 1, NHC_6H_5), 6.7-7.8 (m, 11, C_6H_5 and CHNH?), 5.6 [d of d, 1, J(H-P) = 22 Hz, J(HH) = 10 Hz, CHNH], 3.5-4.6 (m, 4, CH_2CH_3), 1.25 (overlapping triplets, 6, CH_2CH_3).

Anal. Calcd for $C_{18}H_{23}N_2O_4P$: C, 59.66; H, 6.40; N, 7.73; P, 8.55. Found: C, 59.60; H, 6.41; N, 7.65; P, 8.69.

Diphenyl {1-[3-(4-chlorophenyl)ureido]butyl}phosphine Oxide (8). A mixture of 0.15 mol each of *p*-chlorophenylurea, phenyl diphenylphosphinite, and *n*-butyraldehyde in 150 g of toluene was warmed at reflux for 5.5 hr, giving a reaction mixture having a ^{31}P nmr signal only at −36.8 ppm. When the toluene was removed at reduced pressure, the residue solidified. Recrystallization of a portion from benzene gave **8**, a white solid: mp 257-258°; ^{31}P nmr −37.4 ppm; ^{1}H nmr δ 9.1 (s, 1, NHC_6H_4Cl), 6.4-8.1 (m, 15, aryl and CHNH?), 5.1 (m, 1, PCH), 0.6-2.0 (m, 7, $CH_2CH_2CH_3$).

Anal. Calcd for $C_{23}H_{24}ClN_2O_2P$: C, 64.70; H, 5.67; N, 6.56; Cl, 8.30; P, 7.25. Found: C, 65.45; H, 5.62; N, 6.55; Cl, 8.59; P, 7.20.

1-(3,3-Diphenylureido)ethylphosphonic Acid (10a). Freshly distilled acetaldehyde (0.22 mol) was added during 0.5 hr to a stirred solution of 0.1 mol each of 1,1-diphenylurea and triphenyl phosphite in 130 g of benzene at 60°. The solution was warmed at reflux (65-70° with Dry Ice cooled condenser) for 1.25 hr, giving a dark brown solution having a small ^{31}P nmr peak at −126.2 ppm for unreacted phosphite and a large product peak at −18.4 ppm (~1:5 areas). The reaction mixture was stripped to 130° (3 mm). The residue was diluted with 200 ml of acetonitrile and 10 g of H_2O, and this solution was warmed at reflux for 3 hr. Solid that separated during warming was recrystallized from acetic acid-water to give **10a** as a white solid: mp 186-187° dec; ^{31}P nmr −21.6 ppm; ^{1}H nmr δ 10.0 (s, 2, OH), 7.3 (m, 10, C_6H_5), 5.4 (d of d, 1, J = 9, 5 Hz, NH), 4.1 (m, 1, CH), 1.3 (d of d, 3, J = 16 and 7 Hz, CH_3); acidity 2.00 equiv/mol, pK_1 = 2.20, pK_2 = 8.62.

Anal. Calcd for $C_{15}H_{17}N_2O_4P$: C, 56.25; H, 5.35; N, 8.75; P, 9.67. Found: C, 56.43; H, 5.36; N, 8.84; P, 9.60.

[α-(3,3-Dimethylureido)-4-nitrobenzyl]phosphonic Acid (10b). A mixture of 30.2 g (0.2 mol) of 4-nitrobenzaldehyde, 17.6 g (0.2 mol) of 1,1-dimethylurea, and 62.0 g (0.2 mol) of triphenyl phosphite in 100 ml of benzene was warmed at 86-87° for 1.5 hr to give a clear yellow solution: ^{31}P nmr −13.4 (d, J = 23 Hz) and −127.9 ppm (area ratio ~5:1). The reaction mixture was stirred as it cooled, and it was then filtered to give 54.1 g of off-white solid (**9b**), mp 155-170° after recrystallization from acetonitrile. A solution of this solid in acetone-water (10:1) was refluxed for 2 hr and then allowed to stand open to the atmosphere for 10 days. Acetonitrile was added to the residue, and the mixture was warmed to boiling and then filtered while hot to give a yellow solid. Recrystallization once from acetonitrile-ethanol and twice from 2-propanol gave white solid: mp 187-205° dec; ^{31}P nmr (CD_3SOCD_3) −16.4 ppm (d, J = 24 Hz); ^{1}H nmr δ 11.1 (s, 2, OH), 8.1 (d of d, 4, aryl), 6.5 (m, 1, NH), 5.3 (d of d, 1, J = 24, 8 Hz, CH), 2.9 (s, 6, CH_3).

Anal. Calcd for $C_{10}H_{14}N_3O_6P$: C, 39.60; H, 4.65; N, 13.86; P, 10.21. Found: C, 39.68; H, 4.75; N, 14.07; P, 10.38.

Diphenyl[α-(1,3-dimethylureido)benzyl]phosphine Oxide (11). After a solution of 0.5 mol of phenyl diphenylphosphinite, 0.55 mol of benzaldehyde, and 0.25 mol of 1,3-dimethylurea in 150 ml of chlorobenzene had been warmed at 130° for 1 hr, a ^{31}P nmr spectrum of the solution had peaks at −108.3 and −31.5 ppm (~1:1). An additional 0.25 mol of 1,3-dimethylurea was added, and warming at 130° was continued for 2 hr, giving a solution having a ^{31}P nmr signal only at −32.8 ppm. Concentration of the solution to 130° (5 mm) and then dilution of the residue with acetone gave 143 g (75% yield) of **11**. Recrystallization from chlorobenzene gave a white solid: mp 217-220°; ^{31}P nmr −32.6 ppm; ^{1}H nmr δ 7.0-8.1 (m, 15, aryl), 6.7 (d, 1, J = 9 Hz, PCH), 5.1 (q, 1, J = 5 Hz, $NHCH_3$), 3.0 (s, 3, $CHNCH_3$), 2.6 (d, 3, J = 5 Hz, $NHCH_3$); mass spectrum *m/e* 378 (molecular ion).

Anal. Calcd for $C_{22}H_{23}N_2O_2P$: C, 69.83; H, 6.13; N, 7.40; P, 8.18. Found: C, 70.04; H, 6.18; N, 7.28; P, 7.80.

Registry No. *meso*-**1a**, 43077-35-6; *dl*-**1a**, 43077-36-7; *meso*-**1b**, 43077-37-8; *dl*-**1b**, 43077-38-9; *meso*-**1c**, 43077-39-0; *dl*-**1c**, 43077-40-3; **1d**, 43077-41-4; **2**, 43077-42-5; **3a**, 43077-43-6; **4a**, 43077-44-7; **4b**, 43077-45-8; **5a**, 43077-46-9; **5b**, 43077-47-0; **6**, 43077-48-1; **7a**, 43077-49-2; **7b**, 43077-50-5; **7c**, 43077-51-6; **8**, 43077-52-7; **9b**, 43077-53-8; **10a**, 43077-54-9; **10b**, 43077-55-0; **11**, 43077-56-1; urea, 57-13-6; triphenyl phosphite, 101-02-0; acetaldehyde, 75-07-0; benzaldehyde, 100-52-7; tris(2-chloroethyl) phosphite, 140-08-9; thiourea, 62-56-6; *n*-butyraldehyde, 123-72-8; propionaldehyde, 123-38-6; 2-ethylhexaldehyde, 123-05-7; isobutyraldehyde, 78-84-2; ethyl diphenylphosphinite, 719-80-2; ethyl hydantoate, 6293-20-5; 4-chlorophenylurea, 140-38-5; vanillin, 121-33-5; triethyl phosphite, 122-52-1; phenylurea, 64-10-8; 1,1-diphenylurea, 603-54-3; phenyl diphenylphosphinite, 13360-92-4; 1,1-dimethylurea, 598-94-7; 4-nitrobenzaldehyde, 555-16-8; 1,3-dimethylurea, 96-31-1.

References and Notes

(1) E. Fluck, *Top. Phosphorus Chem.*, **4**, 291 (1967).
(2) L. D. Quin, *Top. Phosphorus Chem.*, **4**, 23 (1967).
(3) M. I. Kabachnik, *et al.*, *Russ. Chem. Rev.*, **37** (7), 503 (1968).
(4) K. Moedritzer and R. R. Irani, *J. Org. Chem.*, **31**, 1603 (1966).
(5) J. W. Lyons, "The Chemistry and Uses of Fire Retardants," Wiley-Interscience, New York, N. Y., 1970.
(6) A. Michaelis and R. Kaehne, *Chem. Ber.*, **31**, 1048 (1898).
(7) A. E. Arbuzov, *J. Russ. Phys. Chem. Soc.*, **38**, 687 (1906).
(8) A. E. Arbuzov and L. V. Nesterov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 361 (1954); *Chem. Abstr.*, **49**, 9541 (1955).
(9) G. M. Kosolapoff, "Organophosphorus Compounds," Wiley, New York, N. Y., 1950, Chapter 7.
(10) R. G. Harvey and E. R. DeSombre, *Top. Phosphorus Chem.*, **1**, 57 (1964).
(11) A. J. Kirby and S. G. Warren, "The Organic Chemistry of Phosphorus," Elsevier, Amsterdam, 1967, pp 15, 37.
(12) M. I. Kabachnik, *Z. Chem.*, **2**, 289 (1961).
(13) L. Meites and H. Thomas, "Advanced Analytical Chemistry," Maple Press Co., York, Pa., 1958, pp 12, 88, 97.