Run QY-1: 630.0 mg, no additive, 0.111 mEinstein, 31.0 mg of product, 0.94.

Run QY-2: 355.6 mg, no additive, 0.138 mEinstein, 30.9 mg of product, 0.72.

Run QY-3: 299.4 mg, no additive, 0.850 mEinstein, 55.5 mg of product, 0.39.

Run QY-Q1: 646.1 mg, piperylene, 42.5 g, 0.40 *M*, 0.106 mEinstein, 25.1 mg of product, 0.82.

Run QY-Q2: 639.7 mg, piperylene, 85.7 g, 0.80 *M*, 0.106 mEinstein, 21.3 mg of product, 0.75.

Run QY-Q3: 641.0 mg, piperylene, 139.0 g, 1.30 *M*, 0.107 mEinstein, 19.0 mg of product, 0.65.

Run QY-Q4: 560.0 mg, piperylene, 171.2 g, 1.60 *M*, 0.117 mEinstein, 21.6 mg of product, 0.62.

Run QY-S1: 296.0 mg, acetophenone, 82.3 g, 0.94 *M*, 0.141 mEinstein, 43.0 mg of product, 1.02.

Run QY-S2: 298.6 mg, acetophenone, 82.3 g, 0.94 *M*, 0.194 mEinstein, 52.1 mg of product, 0.90.

Phosphorescence Emission Spectrum of *trans,trans*-2,3-Diphenyl-1-benzoylcyclopropane. The emission spectrum of the ketone was determined on an Aminco-Bowman spectrophosphorimeter in 75:19 methylcyclohexane–isopentane glass at liquid nitrogen temperature at a concentration of 10.0 m*M*. The signal was enhanced using the program XY time averager[22] on a PDP-8/I computer.[23] The spectrum consisted of a progression of bands at 384.4, 410.2, 439.8, 472.2, and 506.6 nm.

Acknowledgment. Support of this research by the Army Research Office (Durham) is gratefully acknowledged. T. W. F. expresses appreciation to the National Science Foundation for a Summer Fellowship (1966) and to the National Institutes of Health for a Predoctoral Fellowship (1966–1969).

(22) This program was written in these laboratories. Special thanks are due to R. McKelvey for performing this experiment.

(23) Digital Equipment Corporation, Maynard, Mass.

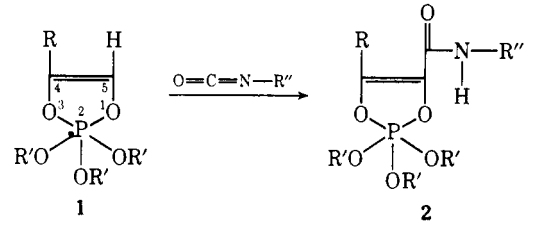
Introduction of the Amide Function into 1,3,2-Dioxaphospholenes with Pentavalent Phosphorus

Fausto Ramirez,[1a] J. Bauer, and C. David Telefus[1b]

Contribution from the Department of Chemistry, State University of New York, Stony Brook, New York 11790. *Received May 7, 1970*

Abstract: Carbamyl-1,3,2-dioxaphospholenes with pentavalent phosphorus were synthesized from α-ketoaldehydes, isocyanates, and trialkyl phosphites. The phospholenes were converted into phosphate esters of β-keto-α-hydroxyamides. These underwent very rapid hydrolyses to β-keto-α-hydroxyamides.

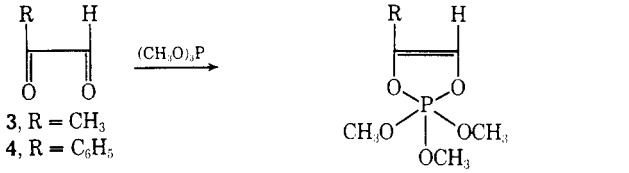
The 2,2,2-trialkoxy-1,3,2-dioxaphospholenes (**1**) are versatile reagents in organic synthesis.[2] They are readily prepared from α-dicarbonyl compounds and trialkyl phosphites.[2] This paper describes a new reaction whose net effect is to replace the hydrogen atom on the phospholene ring by the amide function. The carbamylphospholenes (**2**) are the high-energy orthophosphate esters[3] of the enediol tautomers of β-keto-α-hydroxyamides.



1 2

Results

Reaction of Pyruvaldehyde with Trimethyl Phosphite. Aqueous pyruvaldehyde (**3**) was dehydrated and converted into the phospholene **5** by reaction with trimethyl phosphite. Anhydrous pyruvaldehyde was also made, but less conveniently, from dihydroxyacetone[4] and from acetone.[5]



3, R = CH_3
4, R = C_6H_5

5, R = CH_3; $\delta^{31}P = +44.8$ ppm *vs.* H_3PO_4
6, R = C_6H_5; $\delta^{31}P = +45.4$ ppm

The structure of **5** was based on the ^{31}P nmr shift and on the data of Table I. The molecule is assumed to be a trigonal bipyramid in which case it can exist as three diastereomers,[6] all meso forms. The three methoxy groups of **5** gave one ^1H nmr signal at 20°, and the spectrum did not change at −90°. This pentaoxyphosphorane, as its analogs,[2] undergoes rapid positional exchange of groups by pseudorotation[7] or by other mechanisms.[8]

(1) (a) This work was supported by Public Health Service Grant No. CA-04769-10 from the National Cancer Institute and by the National Science Foundation Grant GP-6690; author to whom correspondence should be addressed; (b) Petroleum Research Fund of the American Chemical Society Fellow.

(2) (a) F. Ramirez, *Accounts Chem. Res.*, **1**, 168 (1968); (b) F. Ramirez, *Bull. Soc. Chim. Fr.*, 2443 (1966); (c) F. Ramirez, *Pure Appl. Chem.*, **9**, 337 (1964).

(3) The ortho state of phosphoric acid is pentahydroxyphosphorane, $(HO)_5P$, in the sense that orthocarbonic acid is $(HO)_4C$ and orthoformic acid is $(HO)_3CH$.

(4) H. O. L. Fischer and L. Feldmans, *Chem. Ber.*, **62**, 864 (1929).

(5) H. L. Riley, J. Morley, and N. A. C. Friend, *J. Chem. Soc.*, 1875 (1932).

(6) There are 20 isomers of P(1, 2, 3, 4, 5) if the five ligands are different but symmetric. Two isomers are excluded in cyclic oxyphosphoranes because the ring cannot be diapical. In the present case, **5**, three ligands are identical, which combined with other symmetry properties of the molecule, results in the three isomers *a*, *j*, *h*. The remaining bipyramids will be equivalent to these three and simply disclose the positional exchange of the groups.

(7) (a) F. Ramirez, J. F. Pilot, C. P. Smith, S. B. Bhatia, and A. S. Gulati, *J. Org. Chem.*, **34**, 3385 (1969); (b) P. C. Lauterbur and F.

Table I. Analyses and Spectral Data[a] of the Products Derived from the Reaction of Trimethyl Phosphite with α-Ketoaldehydes and Isocyanates

α-Keto-aldehyde	Isocyanate	No.	Mp or bp, °C (mm)	Formula	Calcd, % C	H	N	P	Found, % C	H	N	P	τ_{CH_3C}	τ_{H-X}	τ_{CH_3OP}	J_{CH_3OP}, cps	ν, cm^{-1}	λ, mμ	ε × 10^{-3}
													2,2,2-Trimethoxy-1,3,2-dioxaphospholenes						
Py	None	5	26–27 (0.05)	$C_6H_{13}O_5P$	36.7	6.7		15.8	36.3	6.6		16.2	8.12[b]	3.70[c]	6.41	13.2	1700; 1060		
Py	Phenyl	23	101–103[d]	$C_{13}H_{18}O_6NP$	49.5	5.7	4.4	9.8	49.3	5.8	4.5	9.7	7.64	2.25	6.32	13.5	3420; 1700; 1670; 1060	272[e]	17.3
Py	*p*-Tosyl	24	90–91[f]	$C_{14}H_{16}O_8NPS$	42.7	5.1	3.6	7.9	42.5	5.0	3.5	7.6	7.56, 7.74	1.50	6.32	13.2	3340; 1700; 1645; 1030	227;[e] 271	14.1; 9.1
Py	Carbophenoxy	25	96–99[d]	$C_{14}H_{18}O_8NP$	46.8	5.0	3.9		47.2	5.0	3.4		7.64	1.83	6.32	13.2	3311; 1783; 1730; 1695	275[e]	13.0
PG	Carbophenoxy	48	107–110[g]	$C_{19}H_{20}O_8NP$	54.2	4.7	3.3		54.4	4.9	3.3			*h*	6.30	13.1	3378; 1789; 1739; 1645	280; 315	10.8; 8.5
													α-Ketol Phosphates and β-Keto-α-hydroxyamide Phosphates						
Py	None	7	78–79 (0.05)	$C_5H_{11}O_5P$	32.9	6.1		17.0	32.7	6.1		16.8	7.82	5.33[i]	6.16	11.3	1760; 1280; 1030		
PG	None	8	111–112 (0.05)	$C_{10}H_{13}O_5P$	49.2	5.4		12.7	49.0	5.5		12.5		4.71[j]	6.25	11.1			
Py	Phenyl	34	85–86[d]	$C_{12}H_{16}O_6NP$	47.8	5.3	4.6	10.3	48.0	5.3	4.5	10.2	7.61	4.58,[k] 0.92	6.12,[l] 6.16	11.0, 11.0	3420; 1740; 1700	243;[e] 310[m]	12.0
Py	*p*-Tosyl	35	110–111[n]	$C_{13}H_{18}O_8NPS$	41.2	4.8	3.7	8.2	41.5	4.8	3.6	8.0	7.58, 7.74	4.72,[o] −0.63	6.14,[l] 6.25	11.2, 1.0	3320; 1745; 1725	227;[e] 263	14.2; 1.4
Py	Carbophenoxy	36	117–124[d]	$C_{13}H_{16}O_8NP$	45.2	4.6	4.1	8.9	45.5	4.7	3.9	8.5	7.63	4.17, 0.00	6.16,[l] 6.20	11.0, 11.0	3400; 1810; 1770; 1740	238; 270	4.6; 1.4
PG	Carbophenoxy	49	158–165[d]	$C_{18}H_{18}O_8NP$	53.1	4.4	3.4	7.6	53.2	4.5	3.4	7.1		3.33[p]	6.22,[l] 6.50	11.0, 11.0	3378; 1818; 1786; 1754; 1706		
													β-Keto-α-hydroxyamides						
Py	Phenyl	41	Dec										7.46	5.20, 1.30, 5.00[q]			3400; 1720; 1690		
Py	Phenyl	46	98–99[r]	$C_{11}H_{13}O_3N$	63.7	6.3	6.7		63.9	6.3	6.7		7.50, 8.33	1.20, 5.00			3390; 1710; 1695		
Py	*p*-Tosyl	42	93–95[f]	$C_{11}H_{13}ONS$	48.7	4.8	5.1	*s*	48.5	4.9	5.0		7.59, 7.67	5.34, 0.33, 5.20			3420; 3320; 1720	230[t]	15.0
													Enediolamide Ether Phosphate						
Py	*p*-Tosyl	40	124–125[u]	$C_{15}H_{22}O_8NPS$	44.2	5.4	3.4	7.6	44.1	5.4	3.2	7.4	7.56, 7.83[v]	6.18, 6.75	6.20	11.2	1680; 1620	232; 261	16.2; 13.2
													Enediolamide Lactone Phosphate						
Py	Carbophenoxy	47	171–172[w]	$C_7H_{10}O_7NP$	33.5	4.0	5.6	12.3	33.6	3.9	5.6	12.2	7.73[x]		6.10	11.2	3540; 1770; 1730; 1650	237	7.2

[a] The ^{1}H nmr spectra were taken in $CDCl_3$ except as indicated, at 25° at 60 Mcps. The signals are given in parts per million from TMS = 10 (τ values). Signals of aromatic ^{1}H are omitted. All integrated intensities were as expected from the structures given. The ir spectra were taken in CH_2Cl_2. Py = pyruvaldehyde; PG = phenylglyoxal. [b] Doublet, $J_{H-C-C-C-H}$ = 1.8 cps. [c] Doublet of quartets, $J_{H-C-O-P}$ = 34.0 cps; $J_{H-C-C-C-H}$ = 1.8 cps. [d] Benzene–hexane or ether. [e] In CH_3CN. [f] CH_2Cl_2–ether. [g] Ethyl acetate hexane. [h] Hidden under aromatic protons. [i] Doublet, $J_{H-C-O-P}$ = 10.5 cps. [j] Doublet, $J_{H-C-O-P}$ = 10.2 cps. [k] First signal was a doublet, $J_{H-C-O-P}$ = 8.5 cps. Second signal was due to amide N–*H*. [l] Two doublets; the two CH_3O were not magnetically equivalent. [m] Upon addition of $NaOCH_3$. Transient band, returned to original spectrum by HCl. [n] Ethyl acetate. [o] Doublet, $J_{H-C-O-P}$ = 9.0 cps. [p] Doublet, $J_{H-C-O-P}$ = 10.0 cps. [q] The first signals were due to H–C; the second to *H*–N; the third to *H*–O; all singlets. [r] CH_3OH–H_2O. [s] Calcd: S, 11.6. Found: S, 11.6. [t] CH_2Cl_2. [u] Benzene–ether, then ethyl acetate. [v] Doublet, due to long-range coupling $J_{H-C-C-C-C-O-P}$ = 2.2 cps. [w] Acetone–hexane. [x] Doublet, $J_{H-C-C=C-O-P}$ = 2.1 cps.

Reaction of the Phospholenes with Hydrogen Chloride. The phospholene **5** gave dimethyl 2-oxopropylphosphate (**7**) and methyl chloride on treatment with hydrogen chloride. Small amounts of α-chloroacetone (**9**) and trimethyl phosphate (**11**) were formed as by-products. The phospholene **6** made from phenylglyoxal (**4**) and trimethyl phosphite,[9] gave the corresponding dimethyl 2-phenyl-2-oxoethylphosphate (**8**) with hydrogen chloride. A small amount of phenacyl chloride (**10**) was formed as by-product. These products can be explained by the protonation of the phospholenes to give $(RO)(CH_3O)_3P^+Cl^-$ (**12**) followed by attack of chloride on the activated carbon atoms of **12**. The reaction of the phospholenes with hydrogen chloride could, in principle, yield α-hydroxyaldehyde phosphates, $(CH_3O)_2P(O)OCHRCOH$ (**13**), but these substances were not, in fact, observed.

7, R = CH_3; $\delta^{31}P = -0.9$ ppm
8, R = C_6H_5; $\delta^{31}P = -1.3$ ppm

The syntheses of the ketol phosphates **7** and **8** completes the synthesis[10] of the sugar analogs **17–19** from the corresponding phospholenes **14–16**.

14–16 → **17–19**

R = H; R = CH_3; R = C_6H_5

Reaction of the Pyruvaldehyde–Phosphite Adduct 5 with 1 Mol Equiv of Isocyanates. The phospholene **5** reacted with phenyl isocyanate (**20**) to give a crystalline adduct formulated as 2,2,2-trimethoxy-4-methyl-5-phenylcarbamyl-2,2-dihydro-1,3,2-dioxaphospholene (**23**).

To arrive at a structure for the 1:1 adduct **23** let us consider possible reaction mechanisms. The carbon carrying the hydrogen atom in the phospholene **5** should be the nucleophilic site which adds to the electrophilic carbon of the isocyanate **20** to form the dipolar ambident ion **26** (*cf.*, the reaction with HCl). The dipolar ion **26** could close to the iminophospholene **27** which has five oxygen atoms attached to phosphorus. The alternate cyclization of **26** would give a phosphorane (not shown) with one N and four O attached to phosphorus. Due to the lower electronegativity of N *vs.* O and to the larger steric requirements associated with azaphosphoranes *vs.* oxaphosphoranes, the latter are favored over the former, *i.e.*, **27** should be formed. A tautomeric shift of the proton from carbon to nitrogen would yield the phospholenamine **28**.

5 + O=C=N—R →
20, R = C_6H_5
21, R = $SO_2C_6H_4CH_3$-*p*
22, R = —C(=O)—OC_6H_5

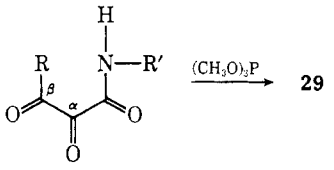
23, R = C_6H_5; $\delta^{31}P = +49.5$ ppm
24, R = $SO_2C_6H_4CH_3$-*p*; $\delta^{31}P = +48.6$ ppm
25, R = —C(=O)—OC_6H_5; $\delta^{31}P = +48.9$ ppm

At the stage of the dipolar ion **26**, the proton can shift from carbon to nitrogen to give a second dipolar ion **29** with considerable resonance stabilization, *i.e.*, a "trident anion" with charges on carbon or on two oxygens. Ring closure of **29** should give the carbamylphospholene **23** and not the phospholenamine **28**.

5 → **26** → **27** ⇌ **28** → **29** ⇌ **28** → **23–25**

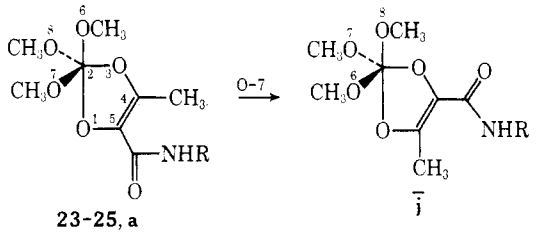
We prefer the carbamylphospholene **23** over the phospholenamine **28** as the structure of the adduct because the former **23** represents the enediolorthophosphate[3] resulting from the reduction of an α,β-diketoamide by trimethyl phosphite: **30** → **29** → **23** – **25**. The phospholenamine **28** would correspond to the reduction of the *α-ketoamide function* of **30**, which we regarded as unfavorable when compared to the reduction of the *vicinal diketone function* of **30**.

Ramirez, *J. Amer. Chem. Soc.*, **90**, 6722 (1968). The literature on pseudorotation was reviewed in these references.
(8) F. Ramirez, *Bull. Soc. Chim. Fr.*, in press.
(9) F. Ramirez, A. V. Patwardhan, and C. P. Smith, *J. Org. Chem.*, **30**, 2575 (1965).
(10) (a) F. Ramirez and N. B. Desai, *J. Amer. Chem. Soc.*, **82**, 2652 (1960); (b) F. Ramirez, A. V. Patwardhan, N. B. Desai, and S. Heller, *ibid.*, **87**, 549 (1965); (c) F. Ramirez, S. L. Glaser, A. J. Bigler, and J. F. Pilot, *J. Amer. Chem. Soc.*, **91**, 496 (1969); *ibid.*, **91**, 5696 (1969) (correction).



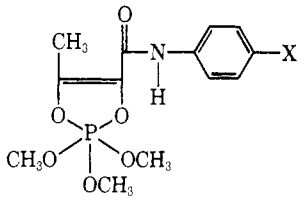
30

These considerations leading to the carbamylphospholene **23** are supported by the nmr, ir, and uv spectra given in Table I. The ^{31}P nmr shift showed that the phosphorus was pentavalent.[2] The ir data were consistent[11] with structure **23**. The band at 1700 cm^{-1} is reasonable for the particular[2] C=C in **23**, while that at 1670 cm^{-1} is expected of an amide. The uv spectrum disclosed a chromophore with considerable degree of conjugation. The ^{1}H nmr signals are in agreement with formula **23** but do not exclude **28**. Note that the three methoxy groups gave one signal in agreement with the existence of a relatively rapid positional exchange of groups in trigonal-bipyramidal phosphorus, perhaps by pseudorotation[7,8] **a** → **j**.



23-25, a

A series of para-substituted phenyl isocyanates was converted into carbamylphospholenes **31–33**.

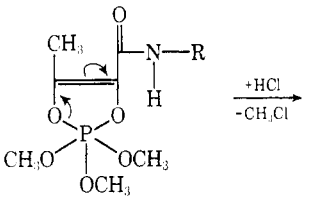


31, X = F; $\delta^{31}P$ = +49.2 ppm
32, X = CN; $\delta^{31}P$ = +49.6 ppm
33, X = OCH_3; $\delta^{31}P$ = +49.5 ppm

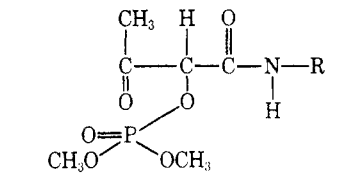
p-Toluenesulfonyl isocyanate (**21**) reacted rapidly with the phospholene **5** to give an adduct **24** of analogous structure. Carbophenoxy isocyanate[12] (**22**) provided the corresponding carbamylphospholene **25**, which was a desirable synthetic intermediate because it contains a removable "masking group" for an amide, namely, the carbophenoxy function

$$R{-}NHCOOC_6H_5 + H_2O \longrightarrow R{-}NH_2 + CO_2 + HOC_6H_5$$

Reaction of the Pyruvaldehyde–Isocyanate–Phosphite Adducts with Hydrogen Chloride. The carbamylphospholenes **23–25** were converted into phosphate esters of β-keto-α-hydroxyamides **34–36** by hydrogen chloride. The conversion of pyruvaldehyde into the phospholene **5** proceeded in quantitative yield. The carbamylphospholenes **23–25** were made in 90% of the theoretical yield. Their conversion into the phosphates **34–36** occurred in 85% of the theoretical yield. The oxyphosphorane condensation is, therefore, a satisfactory route to phosphates of α-hydroxyacetoacetamide.

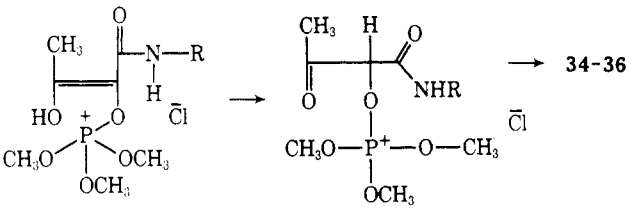


23, R = C_6H_5
24, R = $SO_2C_6H_4CH_3$-*p*
25, R = —C(=O)—OC_6H_5



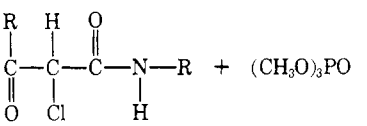
34, R = C_6H_5; $\delta^{31}P$ = +1.0 ppm
35, R = $SO_2C_6H_4CH_3$-*p*; $\delta^{31}P$ = −0.6 ppm
36, R = —C(=O)—OC_6H_5; $\delta^{31}P$ = −0.3 ppm

A possible mechanism for the formation of the phosphates **34–36** involves protonation at one of the oxygens of the dioxaphospholenes **23–25** to give **37**; tautomerization to **38** followed by the loss of methyl chloride leads to **34–36**.



37 **38** → **34-36**

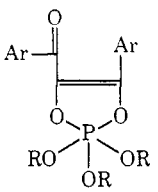
Small amounts of trimethyl phosphate and of what could be the β-ketochloroamides **39** were detected in these reactions.



39

The presence of the group *H*—C—O—*P* was demonstrated by ^{1}H nmr doublets at *ca.* τ 4.2–4.5, with J_{H-P} = 9 cps. The two methoxy groups of the phosphates

(11) The 1:1 adducts made from 1,3-diphenylpropanetrione and trialkyl phosphites were formulated as acylphospholenes.[9] This type of

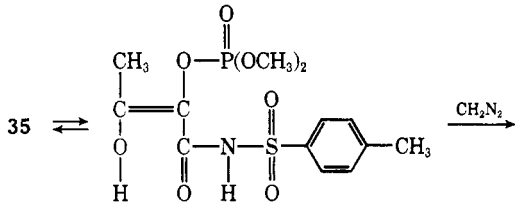


structure resembles the acylphospholenamines **28** more than the carbamylphospholenes, **23–25, 48**. The observed ir spectra of the trione–phosphite adducts were quite different from the spectra of the α-keto-aldehyde–isocyanate–phosphite adducts. This difference favors structures **23–25, 48** over **28** for the latter.

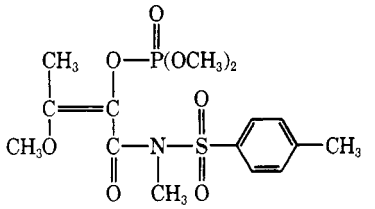
(12) A. J. Speziale, L. R. Smith, and J. E. Fedder, *J. Org. Chem.*, **30**, 4306 (1965).

were not magnetically equivalent due to molecular asymmetry at the α-carbon.

In solutions, the β-keto-α-hydroxyamide phosphates **34–36** are capable of existing in tautomeric equilibrium with the enediol amides, for example **35a**. This was shown by the conversion of the keto form **35** into the enol ether **40** upon treatment with diazomethane. The enol ether was assigned the configuration **40** with the cis relationship of the CH_3– and the phosphate groups. This assignment was based on the observation that the ^1H nmr signal of the CH_3—C=C group gave a doublet, J = 2.2 cps at τ 7.83 ppm. This was attributed to a long-range spin–spin splitting, *H*—C—C=C—O—P. As described below this phenomenon was also observed in a related phosphate ester in which the cis configuration CH_3—C=C—O—P(O)$(OCH_3)_2$ was mandatory.



35a

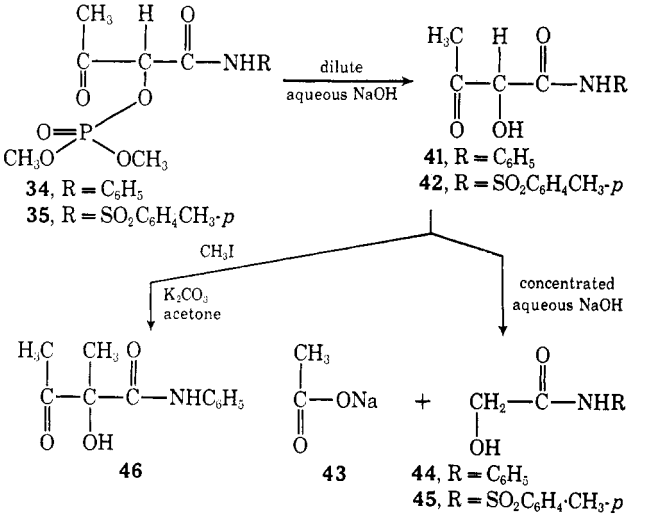


40, $\delta^{31}P$ = +2.2 ppm

Hydrolysis of the β-Keto-α-hydroxyamide Phosphates 34–36. Two of the phosphate esters, **34** and **35**, were converted into the corresponding α-hydroxyacetoacetamides **41** and **42** by 0.3 *N* aqueous NaOH within 2 min at 0°. A possible mechanism for this remarkably rapid hydrolysis will be discussed below.

More severe hydrolytic conditions cleaved **41** and **42** into acetate **43** and the corresponding amides, **44** and **45**, of glyoxylic acid, $HOCH_2COOH$.

One of the α-hydroxyacetoacetamides, **41**, was C alkylated to the α-methyl-α-hydroxyacetoacetamide (**46**).



34, R = C_6H_5
35, R = $SO_2C_6H_4CH_3$-*p*

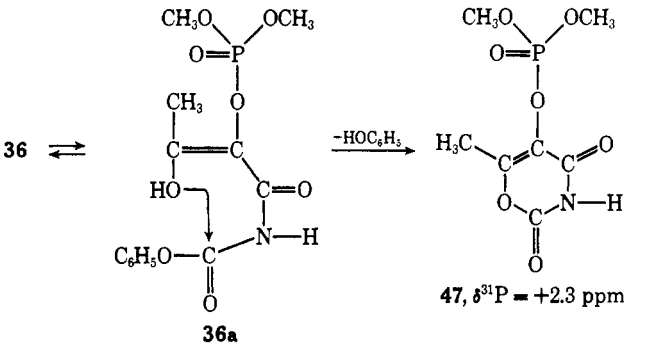
41, R = C_6H_5
42, R = $SO_2C_6H_4CH_3$-*p*

46

43

44, R = C_6H_5
45, R = $SO_2C_6H_4CH_3$-*p*

The phosphate ester **36** derived from carbophenoxyisocyanate underwent primarily a cyclization to the enediol amide lactone phosphate **47** upon treatment with dilute aqueous NaOH. The loss of phenol from **36** and the formation of the lactone **47** was also observed at elevated temperatures, *in vacuo*, in the absence of aqueous alkali. The cyclization of the enol form **36a** to **47** is reasonable.



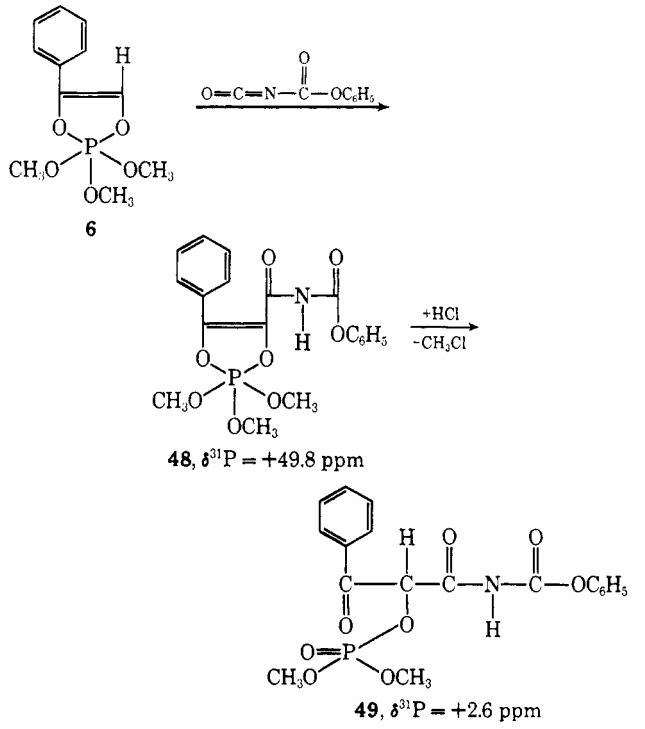
36a

47, $\delta^{31}P$ = +2.3 ppm

Note that the cis configuration CH_3—C=C—O—P(O)$(OCH_3)_2$ is mandatory in lactone **47**. The CH_3 group gave, again, a doublet, J = 2.2 cps in the ^1H nmr, analogous to that observed in the noncyclic analog, **40**.

The two methoxy groups of the phosphate ester in lactone **47** are magnetically equivalent due to molecular symmetry.

Reaction of the Phenylglyoxal–Phosphite Adduct, 6, with 1 Mol Equiv of Carbophenoxy Isocyanate. The phospholene **6** and carbophenoxy isocyanate gave the corresponding carbamylphospholene **48** demonstrating the generality of this type of reaction. Treatment of **48** with hydrogen chloride afforded the phosphate ester of the aromatic β-keto-α-hydroxyamide **49**.



6

48, $\delta^{31}P$ = +49.8 ppm

49, $\delta^{31}P$ = +2.6 ppm

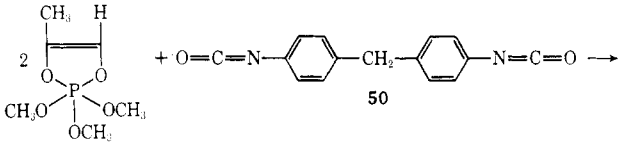
The reaction of the phenylglyoxal–phosphite adduct **6** with 2 mol[13] of phenyl isocyanate was already de-

(13) The enol–hydantoin[14] reacted with a third mole of phenyl iso-

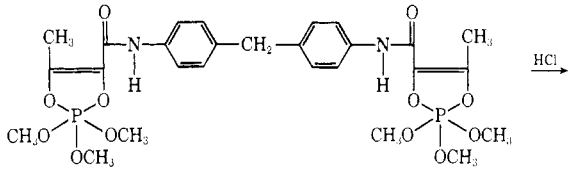
scribed.[14] In that case, the carbamylphospholene analogous to **48** could not be obtained.[13,14] The intermediates in these reactions are sensitive to structural variations which can alter the final outcome of the synthesis.

The reaction of the biacetyl–phosphite adduct **15** with 1 and 2 mol of isocyanates has also been described.[15,16] In this case, the phospholene **15** lacked a hydrogen atom on the ring, which prevented the formation of the carbamylphospholenes **23–25**, **31–33**, and **48**.

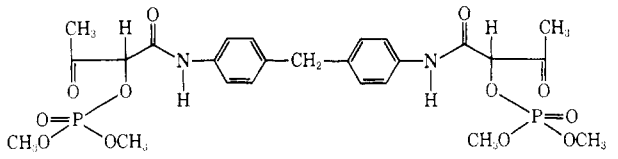
Reaction of 2 Mol of the Pyruvaldehyde–Phosphite Adduct 5 with 1 Mol of a Difunctional Isocyanate. An interesting application of the new oxyphosphorane condensation utilized the available methylenebis(phenyl isocyanate) **50**, which is used in the manufacture of polyurethan foams. The biscarbamylphospholene **51**, and the bisphosphate **52** were formed in satisfactory yields.



5 **50**

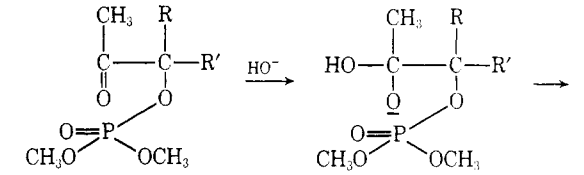


51, $\delta^{31}P = +49.6$ ppm



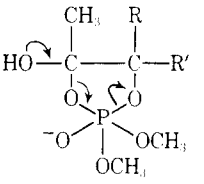
52

Mechanism of the hydrolysis of Phosphate Esters of β-Keto-α-hydroxyamides 34 and **35.** The formation of the intact β-keto-α-hydroxyamides **41** and **42** when the corresponding phosphate esters **34** and **35** were treated with aqueous alkali, is rather striking since these compounds are quite unstable in basic media, as shown by cleavage to acetate ion **43** and the corresponding amides of glyoxylic acid, **44** and **45**, under certain conditions. We suggest that the phosphates **34** and **35** undergo alkaline hydrolysis by a mechanism which involves carbonyl participation to give an intermediate **56**, and oxyphosphorane formation resulting in a second intermediate, **57**.

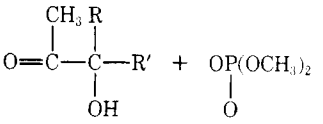


53, R = H; R′ = CONHR″
54, R = H; R′ = CH_3
55, R = CH_3; R′ = COR

56



57



58 **59**

We proposed this mechanism earlier,[17] to account for the observation that the second-order rate constant for the hydroxide ion catalyzed hydrolysis of dimethyl phosphoacetoin (**54**) to acetoin (**58**, R = H; R′ = CH_3) and dimethyl hydrogen phosphate (**59**) was 2 million times larger than the corresponding rate constant for trimethyl phosphate.

The same mechanism, refined[18] by the introduction of the concept of pseudorotation in phosphate hydrolysis,[19] has also been found useful in explaining the course of the hydrolysis of related phosphonate[18] esters derived from acetoin.

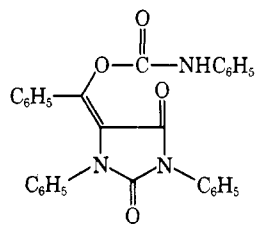
An even more dramatic case of facile hydrolysis of α-keto phosphates is that of the phosphates of diacylcarbinols,[20] **55**. These compounds were converted into the alcohols **58** (R = CH_3; R′ = COR″) by water in boiling benzene. In the present work, it was also possible to effect the hydrolyses of the phosphates (**53**) to the alcohols (**58**, R = H; R′ = CONHR″) by water in refluxing benzene.

Experimental Section

The elemental analyses by Galbraith Laboratories, Inc., Knoxville, Tenn., and by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y., and the spectral data are given in Table I.

Anhydrous Pyruvaldehyde. (A) From Dihydroxyacetone. The ketone (10 g) and P_2O_5 (30 g) were mixed at 20° and *carefully* heated to 80°. Vapors of pyruvaldehyde were *vigorously released* and were condensed in a trap cooled by liquid N_2. The aldehyde was transferred by distillation into a vessel cooled by liquid N_2. The aldehyde was mixed with benzene (5 ml) and this solution was added to trimethyl phosphite at 20° to obtain the phospholene as described below. This procedure was used to obtain the analytical sample of the phospholene **5**; it is not recommended for the preparation of **5** in a large scale.

cyanate to give the *O*-carbamate derivative. This was readily converted into the hydantoin by hot methanol or aqueous dioxane.



(14) F. Ramirez, S. B. Bhatia, C. D. Telefus, and C. P. Smith, *Tetrahedron*, **25**, 771 (1969).
(15) F. Ramirez, S. B. Bhatia, and C. P. Smith, *J. Amer. Chem. Soc.*, **89**, 3030 (1967).
(16) F. Ramirez and C. D. Telefus, *J. Org. Chem.*, **34**, 376 (1969).
(17) F. Ramirez, B. Hansen, and N. B. Desai, *J. Amer. Chem. Soc.*, **84**, 4588 (1962).
(18) D. S. Frank and D. A. Usher, *ibid.*, **89**, 6360 (1967).
(19) (a) F. H. Westheimer, *Accounts Chem. Res.*, **1**, 70 (1968); (b) E. A. Dennis and F. H. Westheimer, *J. Amer. Chem. Soc.*, **88**, 3432 (1966); (c) R. Kluger, F. Kerst, D. Lee, E. A. Dennis, and F. Westheimer, *ibid.*, **89**, 3918 (1967).
(20) (a) F. Ramirez, S. B. Bhatia, A. J. Bigler, and C. P. Smith, *J. Org. Chem.*, **33**, 1192 (1967); (b) F. Ramirez, S. B. Bhatia, and C. P. Smith, *J. Amer. Chem. Soc.*, **89**, 3026 (1967).

(B) From Commercial Aqueous Pyruvaldehyde. The commercial 40% aqueous solution of pyruvaldehyde with $d = 1.4289$ is said to contain 7.93 mmol of aldehyde per milliliter of solution. Five hundred milliliters of this solution was concentrated in a rotary evaporator at 70° (oil pump vacuum). About 220 ml of water was removed in 3 hr. The residue was mixed with benzene (300 ml) and submitted to azeotropic distillation in a Dean–Stark apparatus with return of the benzene to the original flask. Approximately 65 ml of a viscous aqueous phase which contained "polymers" of pyruvaldehyde was removed in 10 hr. The benzene phase was distilled at 760 mm (boiling range 80–90°) and the distillate was kept a few hours in contact with molecular sieves (100 g, no. 4A). The benzene solution was decanted, the sieves were washed with CH_2Cl_2, and the combined organic layer was distilled at 760 mm to give a solution of nearly anhydrous pyruvaldehyde suitable for the reaction with trimethylphosphite to prepare the phospholene **5**.

Reaction of Pyruvaldehyde with Trimethyl Phosphite. Procedure A. The pyruvaldehyde obtained from 10 g of dihydroxyacetone (procedure A) was allowed to react with trimethyl phosphite for 5 min at 20° in benzene solution (5 ml). The solvent and the excess of phosphite were removed below 40° (20 mm). The **2,2,2-trimethoxy-4-methyl-2,2-dihydro-1,3,2-dioxaphospholene (5)** was collected at bp 29–30° (0.05 mm), in 18% of the theoretical yield based on dihydroxyacetone.

Procedure B (Recommended for Large Scale Preparations). The solution of pyruvaldehyde in benzene–CH_2Cl_2 described above was immediately added to trimethyl phosphite (100 ml) at 20°. The mixture was distilled at 20 mm (bath below 50°) to remove solvent and excess of phosphite and then at 0.1 mm to collect the phospholene **5** (about 120 g, boiling range 55–60°). The ^1H nmr spectrum showed the presence of *ca.* 5% of trimethyl phosphate, which did not interfere in most reactions of the phospholene **5**.

Reaction of the Dioxaphospholenes 5 and 6 with HCl. Preparation of α-Ketolphosphates 7 and 8. HCl gas was introduced into a benzene solution of the methyl and phenyl dioxaphospholenes, **5** and **6**, respectively, for about 1 hr. The solvent was evaporated and the residue was fractionally distilled. The first fraction contained the corresponding (lachrimatory) α-chloro ketones, **9**, **10**, and trimethyl phosphate. The second fraction contained the α-ketol phosphates **7** and **8** which were produced in 70% of the theoretical yield.

Reaction of the Pyruvaldehyde–Trimethyl Phosphite Adduct 5 with 1 Mol Equiv of Phenyl Isocyanate (20). A solution of the isocyanate (**20**, 11.9 g) in a mixture of hexane (25 ml) and ether (10 ml) was added to 1 mol equiv of phospholene **5** at 0°. The mixture was kept 12 hr at 0° and 3 hr at −20°. The crystalline **2,2,2-trimethoxy-4-methyl-5-phenylcarbamyl-2,2-dihydro-1,3,2-dioxaphospholene (23)** (28 g, 90% yield) was filtered under N_2, dried at 40° (0.1 mm), and stored under N_2 at 0°. Sometimes, the crude phospholene **23** was contaminated with some trimethyl phosphate which was removed by trituration with cold ether (3 ml/g). The phospholene **23** was recrystallized from benzene–hexane or from relatively large volumes of ether. The data given in Table I were obtained on fresh samples of **23**.

Reaction of the Pyruvaldehyde–Trimethyl Phosphite Adduct 5 with 1 Mol Equiv of Para-Substituted Phenyl Isocyanates. These reactions were carried out in CH_2Cl_2 solution at 0° for 5 hr. The solutions were allowed to reach 20° and the spectral data were obtained within 1 hr. The phospholenes **31**, **32**, and **33** made from *p*-fluoro-, *p*-cyano-, and *p*-methoxyphenylisocyanate, respectively, had a singlet at τ 7.65 ± 0.02 ppm due to the CH_3 group on the phospholene ring; a singlet in the range τ 2.10–2.25 ppm due to the amide proton, and a doublet at τ 6.33 ± 0.02 ppm, $J_{HCOP} = 13.3$ cps due to the $(CH_3O)_3P<$ group. The ir spectra had a band at 3333 cm^{-1} (NH) and bands at 1680 and 1650 cm^{-1} (C=O and C=C region).

The carbamylphospholenes **31–33** were recrystallized from benzene–hexane. The formation of these phospholenes was accompanied by the production of some trimethyl phosphate resulting from a secondary reaction of the phospholene with a second mole of the isocyanate.

Reaction of the Pyruvaldehyde–Trimethyl Phosphite Adduct with 1 Mol Equiv of *p*-Tosyl Isocyanate (21). A solution of the isocyanate (**21**, 14.5 g) in ether (50 ml) was added dropwise (45 min) to a solution of the phospholene (**5**, 1 mol equiv) in ether (50 ml) at −30°, under N_2. The carbamylphospholene **24** crystallized out of the ether within 2 hr at −30°; it was collected under N_2, washed with ether, and dried at 30° and 0.1 mm for 1 hr. **2,2,2-Trimethoxy-4-methyl-5-(*p*-tosylcarbamyl)-2,2-dihydro-1,3,2-dioxaphospholene (24)** was obtained in 90% of the theoretical yield; it was recrystallized from CH_2Cl_2–ether, and was stored unchanged at −30° for several weeks.

Preparation of Carbophenoxy Isocyanate (22). Oxalyl chloride (27.0 g, 213 mmol) was added, slowly, to a solution of *O*-phenoxycarbamate, $C_6H_5OCONH_2$ (24.3 g, 178 mmol) in CH_2Cl_2 (120 ml) at 20°. The mixture was kept 12 hr at reflux; the solvent was removed and the residue was distilled through a 4-in. Vigreux column. **Carbophenoxy isocyanate** (16 g, 55% of the theoretical yield) had bp[21] 66–68° (2 mm). It was immediately dissolved in CCl_4 to avoid polymerization; this solution showed no changes after 6 days at 20°. The ir spectrum (CCl_4) had bands at 2222, 1761, and 1736 cm^{-1}.

Reaction of aniline with carbophenoxyisocyanate in CCl_4 solution gave *N*-carbophenoxy-*N'*-phenylurea,[21] $C_6H_5OCONHCONHC_6H_5$, in 80% of the theoretical yield. The ir spectrum (CH_2Cl_2) had bands at 1724 and 1701 cm^{-1}.

Reaction of the Pyruvaldehyde–Trimethyl Phosphite Adduct 5 with 1 Mol Equiv of Carbophenoxy Isocyanate (22). (A) In CH_2Cl_2–CCl_4 Solution. The isocyanate **22** (3 g) in CCl_4 (10 ml) was added over a 30-min period to a solution of the phospholene **5** (3.63 g, 1 mol equiv) in CH_2Cl_2 (20 ml) at −60°. The solution was stirred 15 min at −30° and 20 min at 20°. The spectral data (Table I) showed complete reaction to **25**. The solution of **2,2,2-trimethoxy-4-methyl-5-carbophenoxycarbamyl-2,2-dihydro-1,2,3-dioxaphospholene (25)** in CH_2Cl_2–CCl_4 was diluted with benzene (100 ml) and treated with HCl gas at 0° to give the β-keto-α-hydroxyamide phosphate **36** in 70% of the theoretical yield (see below).

(B) In Ether Solution. The isocyanate **22** and the phospholene **5** were combined in ether solution at −40°. The **carbamylphospholene 25** crystallized from the ether and was filtered under N_2 and dried at 0.1 mm; it was isolated in 75% of the theoretical yield.

Reaction of Pyruvaldehyde–Isocyanate–Trimethyl Phosphite Adducts 23–25, with Hydrogen Chloride. The carbamylphospholenes **23–25** were dissolved in benzene (1 *M* solution) and the solutions were treated with HCl gas at 0° for 30 min. The benzene was evaporated and the residues were kept 24 hr under ether at 0° to obtain the ***N*-phenyl-, *N*-*p*-tosyl-, and *N*-carbophenoxy-α-hydroxyacetoacetamide dimethyl phosphate (34–36**, respectively) in 80% theoretical yield.

Reaction of *N*-*p*-Tosyl-α-hydroxyacetoacetamide Dimethyl Phosphate (35 ⇄ 35a) with Diazomethane. The phosphate (**35**, 3 g) was suspended in ether (15 ml) and treated with etheral diazomethane at 20°. Rapid evolution of N_2 led to a clear solution, from which a slower evolution of N_2 was noted. ***N*-*p*-Tosyl-*N*-methyl-α-hydroxy-β-methoxycrotonamide dimethyl phosphate (40)** crystallized from the solution at −30°; it was obtained in 70% of the theoretical yield.

Hydrolyses of β-Keto-α-hydroxyamide Dimethyl Phosphates 34, 35 to β-Keto-α-hydroxyamides 41, 42, and to Dimethyl Hydrogen Phosphate. (a) The phosphate esters **34** and **35** were dissolved in 0.5 *N* aqueous NaOH at 0°. The clear solutions were acidified with 5 *N* aqueous HCl, after 3 min. The ketol amides **41** and **42** precipitated from the aqueous acid and were extracted into CH_2Cl_2. The CH_2Cl_2 solutions were washed with water, dried over Na_2SO_4, and evaporated to give **41** and **42** in 65% of the theoretical yield. Crystalline **N-phenyl-** and ***N*-*p*-tosyl-α-hydroxyacetoacetamide (41** and **42)** can be stored at 0° for several weeks without significant changes. However, these compounds decomposed rapidly at 20°, in the solid state and in CH_2Cl_2 solutions.

(b) Aqueous NaOH (0.8 *N*) and concentrated NH_4OH also converted the ketol amide phosphates **34** and **35** into the ketol amides **41** and **42** within 2 min at 0°. However, higher temperatures and hydroxide concentration, and longer reaction times caused the cleavage of the ketol amides **41** and **42** to acetic acid and the glyoxamides **44** and **45** as described below.

(c) The *N*-phenyl- and the *N*-*p*-tosyl-β-keto-α-hydroxyamide phosphates **41** and **42**, were dissolved in benzene containing 4 mol equiv of water. The mixtures were kept 10 hr at reflux and evaporated. The residues were extracted into $CDCl_3$ and the solutions analyzed by H nmr spectrometry; they contained the β-keto-α-hydroxyamides **44** and **45**, in *ca.* 40% of the theoretical yield.

Hydrolytic Cleavage of β-Keto-α-hydroxyamide Phosphates Acetic Acid and Glyoxamides. The phosphate esters **34** and **35** were dissolved in 6 *N* aqueous NaOH. The solutions were kept 20 min at 20°, acidified with HCl, and extracted with $CHCl_3$ or $CDCl_3$.

(21) Reference 12 gives a different boiling point for carbophenoxy isocyanate. Our preparation had bp 42–43° (0.4 mm). The ir data were in agreement with the structure of the isocyanate. The analytical data of the urea derivative confirmed the structure.

The formation of acetic acid, dimethyl hydrogen phosphate, and the corresponding α-hydroxyamides, glyoxanilide (**44**) from **34**, and *N*-*p*-tosylglyoxamide (**45**) from **35** was demonstrated by ^{1}H nmr spectrometry and by the isolation of the amides.

The ^{1}H nmr spectrum of glyoxanilide (**44**) had singlets at τ 5.92 (CH_2), 4.90 (HO), and 1.25 (NH) ppm in $CDCl_3$. *N*-*p*-Tosylglyoxamide **45** had singlets at: τ 6.12 (CH_2OH) and 7.65 ($CH_3C_6H_4$) ppm (CD_3–SO–CD_3) in addition to the signal of the aromatic protons. The ir spectrum had bands at 3448 and 1730 cm^{-1} (CH_2Cl_2).

Reaction of *N*-Phenyl-α-hydroxyacetoacetamide (41) with Methyl Iodide. The amide **41** (1 g), methyl iodide (2 ml), acetone (5 ml), and K_2CO_3 (1 g), were mixed and kept for 12 hr at reflux temperature. The acetone was evaporated and the residue was extracted with CH_2Cl_2. The CH_2Cl_2 solution was evaporated and the residue was recrystallized from methanol–water. The properties of ***N*-phenyl-α-methyl-α-hydroxyacetoacetamide** (**46**) are given in Table I. The amide was obtained in 60% of the theoretical yield; it can be submitted to short-path distillation under high vacuum without decomposition.

Similar results were obtained when the phosphate ester, **34**, was allowed to react with methyl iodide under analogous conditions. The products were the *C*-methylated ketol amide **46** and dimethyl hydrogen phosphate.

Thermal Decomposition of *N*-Carbophenoxy-α-hydroxyacetoacetamide Dimethyl Phosphate (36). The phosphate **36** (770 mg) was kept for 35 min at 135° (0.2 mm). Phenol condensed in a trap. The residue was crystallized from ether (5 ml) and CH_2Cl_2 (2 ml) to give 130 mg of **5-hydroxy-6-methyl-2,4-dioxo-3,4-dihydro-1,3,2-oxazine dimethyl phosphate** (**47**).

Hydrolysis of *N*-Carbophenoxy-α-hydroxyacetoacetamide Dimethyl Phosphate (36). The phosphate (460 mg) was dissolved in 0.12 *N* aqueous NaOH (20 ml) at 20°. The solution was made acidic with concentrated HCl after 5 min and was extracted with four 15-ml portions of CH_2Cl_2. Removal of CH_2Cl_2 left a mixture of phenol and the **enediolamide lactone phosphate** (**47**). The lactone (140 mg) was freed from the phenol by extraction of the latter into ether. The aqueous layer from the CH_2Cl_2 extraction was evaporated and afforded a second crop of the lactone.

Reaction of the Phenylglyoxal–Trimethyl Phosphite Adduct 6 with 1 Mol Equiv of Carbophenoxy Isocyanate 22. A solution of the phospholene[9] **6** (4.72 g) in methylene chloride (10 ml) was added slowly (20 min) to a *freshly prepared* solution of the isocyanate **22** (3 g; 1 mol equiv) in methylene chloride (10 ml) at −25°. The mixture was stirred for 20 min at −25°, 25 min at 0°, and 1 hr at 20°. The solvent was removed at 20 mm. The residue was triturated with ether (70 ml) and the ether-insoluble **2,2,2-trimethoxy-4-phenyl-5-(carbophenoxycarbamyl)-2,2-dihydro-1,3,2-dioxaphospholene** (**48**) was filtered (5.2 g; 68% of the theoretical yield).

Reaction of the Phenylglyoxal–Carbophenoxy Isocyanate–Trimethyl Phosphite Adduct 48 with Hydrogen Chloride. A solution of the carbamylphospholene **48** (2.5 g) in a mixture of benzene (20 ml) and methylene chloride (15 ml) was treated with HCl gas at 0°. The solution was evaporated and the residue (1.7 g) was treated with ether (20 ml). The ether-insoluble portion (1.7 g) was recrystallized once from benzene and once from benzene–ethyl acetate to give *N*-carbophenoxy-α-hydroxy-α-benzoylacetamide dimethylphosphate (**49**), mp 158–165° in 35% of the theoretical yield.

The ether-soluble material described above was recovered by evaporation and the residue was triturated with cold ether giving *N*-carbophenoxy-α-chloro-α-benzoylacetamide in about 15% of the theoretical yield; this was not studied further.

Reaction of 2 Mol of the Pyruvaldehyde–Trimethyl Phosphite Adduct with 1 Mol of Methylenebisphenyl Isocyanate (50). (a) The phospholene **5** (2 mol) was added to commercially available $OCNC_6H_4CH_2C_6H_4NCO$ (1 mmol) in *CCl_4 solution* at 20°. The ^{31}P nmr of the solution after 24 hr showed nearly complete reaction; $\delta^{31}P = +49.6$ ppm for the biscarbamylphospholene (**61**). Removal of CCl_4 left a powder which was insoluble in ether but soluble in benzene.

(b) The phospholene **5** (2 mol) was added to the bisisocyanate (**50**, 1 mol) in *ether solution* at 20°. After 24 hr at 20°, and 5 hr at 0°, a powder had precipitated out of the ether. It was dissolved in benzene and reprecipitated by ether. The bisphospholene **51** was dried at 60° (0.1 mm).

Anal. Calcd for $C_{27}H_{36}O_{12}N_2P_2$: C, 50.5; H, 5.6; N, 4.4. Found: C, 48.7; H, 4.7; N, 4.9.

The uv spectrum of **51** in acetonitrile had λ_{max} 275 mμ, ε 36,000. The ir spectrum in CCl_4 had bands at 3430, 1690, 1650, and 1080 cm^{-1}. The ^{1}H nmr spectrum in $CDCl_3$ had signals at τ 2.30 (NH), 6.08 (CH_2), 6.33, J_{HP} = 13.2 cps, and 7.65 (CH_3CO) ppm.

Reaction of the Pyruvaldehyde–Methylenebisphenyl Isocyanate Adduct (51) with Hydrogen Chloride. The **bisphospholene 51** was dissolved in benzene as in dioxane. The solution was treated with HCl gas at 20°. The bisphosphate **52** was obtained as a viscous oil by removal of the solvent. The ^{1}H nmr spectrum in $CDCl_3$ had signals at τ 0.92 (NH), 4.62, J_{HP} = 9.0 cps (H–C–O–P), doublet at 6.12, J = 11 cps, doublet at 6.22, J = 11 cps (nonequivalent CH_3OP), singlet at 6.13 (CH_2), singlet at 7.65 (CH_3CO) ppm.