Reactions of Carbonyl Compounds with Tervalent Phosphorus Reagents. Part 7.[1] Benzaldehyde with Chlorodiphenylphosphine in the Presence of Acetic Acid

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The reaction of chlorodiphenylphosphine (1a) with benzaldehyde in the presence of acetic acid has been re-examined. The final products have been isolated and identified as α-acetoxybenzyldiphenylphosphine oxide (4) and bis-α-(diphenylphosphinoyl)benzyl ether (5). The relative amounts of (4) and (5) formed are markedly influenced by the proportion of aldehyde in the reaction mixture.

IN 1923, Conant and his colleagues[2] reported the isolation of an unspecified amount of a white, crystalline solid, m.p. 230°, considered to be α-hydroxybenzyldiphenylphosphine oxide (2), from the reaction of an equimolar mixture of chlorodiphenylphosphine (1a), acetic acid, and benzaldehyde at room temperature. Over thirty years later, Miller and his co-workers repeated Conant's reaction, in connection with a study of the addition of secondary phosphine oxides to aldehydes and ketones,[3] and obtained a solid, m.p. 178°. Detailed evidence[3] showed that this solid was the oxide (2) and this structural assignment has since been confirmed by various workers.[4]

As part of our study of halogenophosphine–aldehyde reactions,[5] we have reinvestigated the chlorodiphenylphosphine–acetic acid–benzaldehyde system. We found that the α-hydroxybenzylphosphine oxide (2) can be obtained conveniently, and in a pure state, by precipitation from a solution of the reactants in chloroform. Our yields are not very high, but are, nevertheless, generally higher than those described earlier.[3] A ^{1}H n.m.r. spectrum of the solution phase of a reaction mixture in deuteriochloroform indicated that acetyl chloride was present in large amounts, together with acetic acid, α-chlorobenzyl acetate (3), some dissolved phosphine oxide (2) and unchanged aldehyde. Presumably the ester (3) was formed by addition of acetyl chloride to benzaldehyde † (Scheme 1).

Rather surprisingly, we noticed that when an equimolar mixture of chlorodiphenylphosphine (1a), acetic acid, and benzaldehyde in chloroform was set aside for a longer period (ca. 3 days), the α-hydroxybenzylphosphine oxide (2) precipitate redissolved. On work-up, a gum was obtained, consisting mainly of two organophosphorus compounds, in ca. 55 : 45 molar ratio, which were separated by preparative t.l.c. on silica gel. The component with the higher R_F value had properties (m.p. and i.r. and ^{1}H n.m.r. spectra) identical with those of authentic α-acetoxybenzyldiphenylphosphine oxide

(4) prepared by reaction of acetoxydiphenylphosphine (1b) with benzaldehyde.[7]

On the basis of analytical and spectroscopic evidence we believe that the second organophosphorus product is
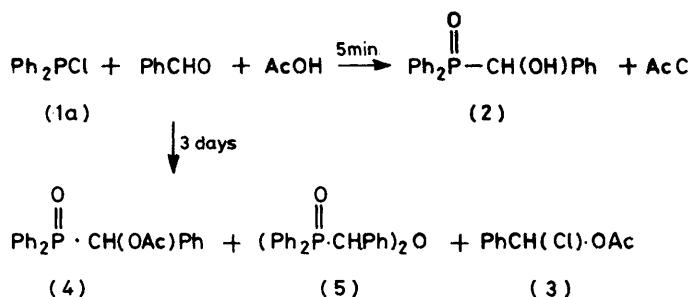
SCHEME 1 Products formed by reaction of chlorodiphenylphosphine with benzaldehyde in the presence of acetic acid

bis-α-(diphenylphosphinoyl)benzyl ether (5). Thus i.r. (ν 1 195 cm^{-1}) and ^{31}P n.m.r. (δ −28 p.p.m.) data indicate that the compound is a phosphine oxide.[8] The ^{1}H n.m.r. spectrum has signals in the aromatic region and a doublet at δ 5.05. The chemical shift and
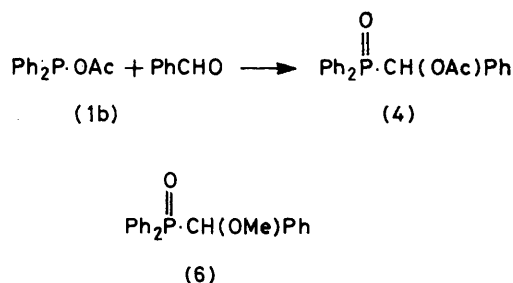
coupling constant (J 8.8 Hz) of the aliphatic resonance are consistent with the partial structure, Ph$_2$P(O)·CHPh·O−, such as exists in α-methoxybenzyldiphenylphosphine oxide (6), for which the methine proton absorbs at δ 5.07 (J 11 Hz). In addition, two of the higher-mass peaks in the mass spectrum, viz. m/e 492 and 397, are assignable to the ions (7) and (8), respectively (Scheme 2), suggesting that the parent ion

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† The ester (3) has been prepared by reaction of benzaldehyde with acetyl chloride.[6]

[1] Part 6, N. J. De'ath, S. T. McNeilly, and J. A. Miller, J.C.S. Perkin I, 1976, 741.

[2] J. B. Conant, J. B. S. Braverman, and R. E. Hussey, J. Amer. Chem. Soc., 1923, 45, 165.

[3] R. C. Miller, C. D. Miller, W. Rogers, and L. A. Hamilton, J. Amer. Chem. Soc., 1957, 79, 424.

[4] R. S. Marmor and D. Seyferth, J. Org. Chem., 1969, 34, 748; T. Emoto, H. Gomi, M. Yoshifuji, R. Okazaki, and N. Inamoto, Bull. Chem. Soc. Japan, 1974, 47, 2449.

[5] (a) J. A. Miller and M. J. Nunn, J.C.S. Perkin I, 1976, 535; (b) N. J. De'ath, J. A. Miller, and M. J. Nunn, Tetrahedron Letters, 1973, 5191.

[6] J. K. Michie, unpublished observations; cf. E. K. Euranto and L. M. Hautoniemi, Acta Chem. Scand., 1970, 24, 50.

[7] M. P. Savage and S. Trippett, J. Chem. Soc. (C), 1966, 1842.

[8] L. C. Thomas, ' The Identification of Functional Groups in Organophosphorus Compounds,' Academic Press, London, 1974, pp. 23—32.

contains two Ph_2PO units and two PhCHO units. The total absence of any peak(s) at higher m/e value(s), e.g. at m/e 598 (even in a 20 eV spectrum) is rather surprising, although microanalytical data accord well with the molecular formula $C_{38}H_{32}O_3P_2$.

Furthermore, a proton noise-decoupled ^{13}C n.m.r. spectrum confirms that there are two equivalent, aliphatic carbon atoms, δ 79.38, in the molecule, each coupled with two phosphorus atoms; the PC coupling constants (88 and 12 Hz) are entirely consistent with
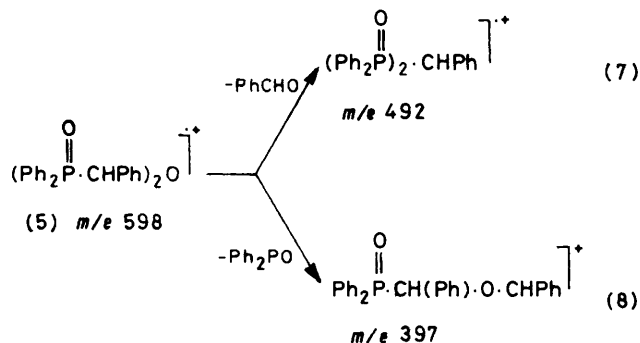
Scheme 2   Mass spectral fragmentation of the ether (5)

one-bond $(^1J_{PC})$ and three-bond $(^3J_{PC})$ coupling,[9] as in the spectrum of (6) where the PC coupling constants for the methine carbon (δ 83.55) and methyl carbon (δ 58.51) are 89 and 13.7 Hz, respectively.

Structure (5) for this product was finally confirmed by its synthesis from diphenylphosphine oxide (9) and the chloro-ether (10), which is produced by reaction of chlorodiphenylphosphine (1a) with benzaldehyde[5b] (Scheme 3). The one feature of the structure of (5) about which there remains some doubt is the stereochemistry. It is not unreasonable to suppose, in the first instance, that (5) would be formed as a mixture of meso- and ($\pm$)-isomers. However, the available evidence, particularly ^{13}C n.m.r. data and m.p., indicates that the purified product is one isomer only. Moreover, there is no evidence from the initial reaction mixture, or from the crude product, that our purification procedure has led to the isolation of one isomer from two originally formed. It is also noteworthy that the synthetic sequence from the chloro-ether (10) (Scheme 3) appears to produce the same single diastereoisomer of (5). This may reflect the fact that (10) is one isomer, but may on the other hand mean that the displacement of the chlorine is controlled by steric factors in the ether product. Further speculation on this point seems inappropriate without additional experimental evidence.

In the light of the above results, the ' white crystals ' obtained in Conant's experiment were probably bis-α-(diphenylphosphinoyl)benzyl ether (5). Not only does this have a similar m.p. to Conant's product, but it also gives a very similar phosphorus analysis.

The relative amounts of (4) and (5) produced in this system are greatly affected by the molar ratio of the reactants. Thus, when 100 mol % excess of benzaldehyde was used, the crude product contained hardly

any of the α-acetate (4). An analogous enhancement of the proportion of the ether (5) was noticed in experiments with suspensions of the phosphine oxide (2) in solutions of acetyl chloride (1 mol. equiv.) in deuteriochloroform. With 1 mol. equiv. of benzaldehyde present at the outset, the ether (5) was virtually the only phosphorus-containing substance in the clear solution produced after 4 days. If no aldehyde was added to the mixture, the products (4) and (5) were obtained in roughly equal amounts in the same period of time.

As regards the nature of the process(es) whereby the phosphine oxides (2), (4), and (5) are produced, our experimental observations do not permit a detailed mechanistic interpretation. Nevertheless, a number of pertinent comments can be made.

First, it seems clear that both products (4) and (5) are formed irreversibly via competitive pathways, each of which is slower than that leading to α-hydroxybenzyldiphenylphosphine oxide (2). Moreover, the fact that the production of (5) relative to (4) is favoured by the presence of benzaldehyde suggests that ' free ' aldehyde is essential to the process whereby (5) is formed. Hence, we may infer that dissociation of (2) to benzaldehyde and diphenylphosphine oxide (9) occurs under the reaction conditions, since (5) is obtained from (2) and acetyl chloride, even in the absence of added aldehyde. Indeed, the detection of α-chlorobenzyl acetate (3) in this reaction indicates that this dissociation is highly likely.

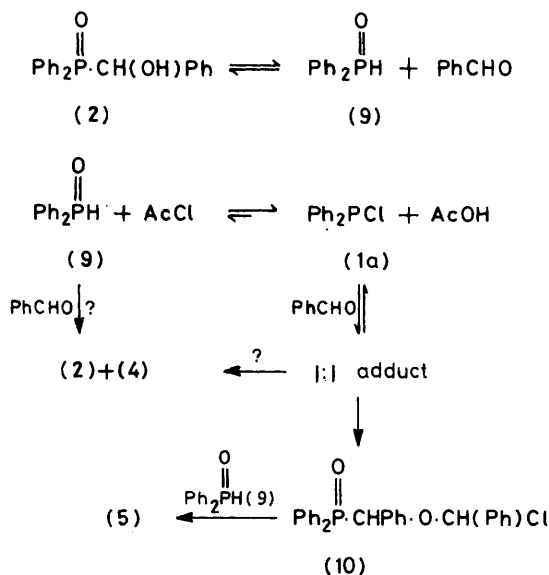The relationship between the dissociation of α-hydroxybenzyldiphenylphosphine oxide (2) and the
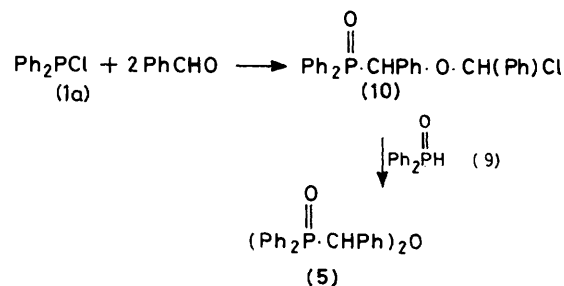
Scheme 3

pathway to the ether (5) became clearer when we studied the reaction between acetyl chloride and diphenylphosphine oxide (9). This produces acetic acid and chlorodiphenylphosphine (1a), in an equilibrium mixture of which acetic acid and (1a) represent about 80% at 20 °C. Equilibrium is achieved in less than 15 min, and the mixture was unchanged during a further 2 h. Thus, the effect of dissociation of (2), in the presence of acetyl chloride, would be to regenerate benzaldehyde and (1a). These two substances are known to react readily at room temperature to produce the 2 : 1 adduct (10),[5b] which, in the present circumstances, could react further with (9) (or its equivalent) to yield (5) (Scheme 4). The stereochemical evidence

[9] L. D. Quin, M. D. Gordon, S. O. Lee, Org. Magnetic Resonance, 1974, 6, 503; T. A. Albright, W. J. Freeman, and E. E. Schweizer, J. Amer. Chem. Soc., 1975, 97, 2942.

discussed above is further reason to regard this pathway to (5) as highly likely.

The pathway by which α-hydroxybenzyldiphenyl-phosphine oxide (2) is formed is by no means clear. For example, it could be produced directly by reaction of benzaldehyde with diphenylphosphine oxide (9).

$$Ph_2P\cdot CH(OH)Ph \rightleftharpoons Ph_2PH + PhCHO$$
(2) (9)

$$Ph_2PH + AcCl \rightleftharpoons Ph_2PCl + AcOH$$
(9) (1a)

(2)+(4) ←—?— 1:1 adduct

$$(5) \xleftarrow{Ph_2PH(9)} Ph_2P\cdot CHPh\cdot O\cdot CH(Ph)Cl$$
(10)

SCHEME 4

Alternatively it may be the result of interaction between acetic acid and a 1 : 1 adduct of benzaldehyde and (1a). Similarly, there are a number of possible routes from reactants to the α-acetate (4).

EXPERIMENTAL

I.r. spectra were recorded on a Perkin-Elmer 157G spectrometer and ^{1}H n.m.r. spectra on a Perkin-Elmer R10 instrument, with tetramethylsilane as internal reference. Solvents used as reaction media were dried and reactions were carried out under dry nitrogen. Benzaldehyde and chlorodiphenylphosphine (m.p. ca. 22—24°) were re-distilled and stored at − 10 °C under dry nitrogen. Acetic acid and acetyl chloride were redistilled.

Reactions of Benzaldehyde with Chlorodiphenylphosphine and Acetic Acid.—(a) *Isolation of α-hydroxybenzyldiphenyl-phosphine oxide* (2). A mixture of benzaldehyde (3.0 g, 28.3 mmol) and glacial acetic acid (1.7 g, 28.3 mmol) was added in one portion to a stirred, cooled (<15 °C) solution of chlorodiphenylphosphine (6.2 g, 28.0 mmol) in chloro-form (15 ml). After 5 min, light petroleum (30 ml) was added, and the white solid which had precipitated in 30 min was filtered off and washed with chloroform to give the oxide (2) (2.7 g, 32%), m.p. 177° (lit.,[3] 178—179.5°); $v_{max.}$ (mull) 3 200 and 1 164 cm^{-1}; δ (CDCl$_3$) 4.1 (d, J 8.4 Hz, variable). A second portion (1.2 g) of the product was obtained by dilution of the filtrate with light petroleum.

(b) *Isolation of α-acetoxybenzyldiphenylphosphine oxide* (4). Chlorodiphenylphosphine (2.5 g, 11.3 mmol), benz-aldehyde (1.33 g, 12.5 mmol), and acetic acid (0.69 g, 11.5 mmol) were mixed in chloroform (12 ml) as in (a). After 4 days at room temperature, the solution was washed with

[10] S. Inokawa, Y. Tanaka, H. Yoshida, and T. Ogata, *Chem. Letters*, 1972, 469.

portions of water, aqueous sodium hydrogen carbonate, and, finally, water again. Drying (MgSO$_4$) and evaporation afforded a gum (4.5 g); a ^{1}H n.m.r. spectrum showed that it consisted mainly of (4) and (5) in the molar ratio ca. 55 : 45. Attempts to separate these by crystallisation and column chromatography on silica were only partially successful. A portion of the material (0.2 g) was separated by multiple elution (70% chloroform–petroleum) on silica preparative t.l.c. plates; the upper band yielded fairly pure α-acetate (4) [0.06 g, equivalent to ca. 34%, based on (1a)], m.p. 168—169° (from petroleum–benzene) (lit.,[7] 171—172°); the lower band yielded rather impure bisphos-phinoylbenzyl ether (5) [see experiment (c)].

(c) *Isolation of bis-α-(diphenylphosphinoyl)benzyl ether* (5). Chlorodiphenylphosphine (1a) (3.69 g, 16.7 mmol), benz-aldehyde (3.54 g, 16.7 mmol), and acetic acid (1.02 g, 17.0 mmol) were mixed in chloroform (10 ml) as in (a). Work-up after 2 days as in (b) afforded a viscous gum, which partially crystallised, and consisted largely of the ether (5) (^{1}H n.m.r.). A crystalline *sample* of (5) (2 g, 40%) was obtained by trituration of the gum with ether, and re-crystallisation of the solid residue from benzene–light petroleum (b.p. 60—80 °C); m.p. 237—238° (Found: C, 75.9; H, 5.35; P, 10.55. C$_{38}$H$_{32}$P$_2$O$_3$ requires C, 76.25; H, 5.4; P, 10.35%); m/e 492, 397, 325 [Ph$_2$P(O)P(O)Ph$^+$], 291 [Ph$_2$P(O)CHPh$^+$], 273 [PhCH(OH)CPh$_2^+$], 255 (Ph$_2$C:CPh$^+$), 183 (Ph$_2$COH$^+$), and 167 (100%, Ph$_2$CH$^+$); δ$_H$ (CDCl$_3$) 6.7—8.1 (m) and 5.05 (1 H, d, J 8.8 Hz); δ$_C$ (CDCl$_3$) 79.38 (dd, $^1J_{PC}$ 88, $^3J_{PC}$ 12 Hz) (p.p.m. downfield from tetramethylsilane); δ$_P$ −28.0 (p.p.m. downfield from 85% phosphoric acid); $v_{max.}$ 1 195 cm^{-1}.

(d) *Reaction in deuteriochloroform.* To chlorodiphenyl-phosphine (0.234 g, 1.06 mmol) was added a mixture of benzaldehyde (0.225 g, 2.12 mmol) and acetic acid (0.064 g, 1.07 mmol) in deuteriochloroform (0.5 ml). Heat was generated and after a few minutes a white precipitate appeared. At this stage (ca. 10 min) the mixture was filtered into an n.m.r. tube; a spectrum of the filtrate exhibited signals corresponding to benzaldehyde [δ 10.1 (s)] (ca. 55% consumed), acetyl chloride [δ 2.57 (s)], and small amounts of acetic acid [δ 2.05 (s)], α-chlorobenzyl acetate (3) [δ 2.17 (s)], and the α-hydroxyphosphine oxide (2) [δ 6.0 (d, J ca. 8 Hz)].

Synthesis of α-Acetoxybenzyldiphenylphosphine Oxide (4).[7] —Acetoxydiphenylphosphine (1b) was prepared by stirring a suspension of anhydrous sodium acetate in an ethereal solution of chlorodiphenylphosphine (<1 mol. equiv.) for 6 h at room temperature, then removing the solids and rapidly evaporating off the ether (reduced pressure). The resulting oil, δ (CDCl$_3$) 2.19br (s, J ca. 1 Hz) [lit.,[10] δ (C$_5$D$_5$N) 2.04 (d, J 1.2 Hz)]; $v_{max.}$ 1 736 cm^{-1} (lit.,[10] 1 750 cm^{-1}), was used without purification.

A solution of the acetate (1b) (1.47 g, 6 mmol) and benz-aldehyde (0.64 g, 6 mmol) in 15% methylene chloride–light petroleum (12 ml) was stirred slowly for 1 day at room temperature. The solid precipitated was the phosphine oxide (4) (0.78 g, 37%), m.p. 168—170° (light petroleum–benzene) (lit.,[7] 171—172°); $v_{max.}$ 1 748 cm^{-1}; δ (CDCl$_3$) 1.98 (3 H, s), 6.80 (1 H, d, J 4.5 Hz); δ$_C$ (CHCl$_3$) 20.7, 73.0 (d, J 84 Hz), and 169.2 (d, J 6 Hz); δ$_P$ (CHCl$_3$) −46.5 (downfield from 85% phosphoric acid).

Reaction of α-Hydroxybenzyldiphenylphosphine Oxide (2) *with Acetyl Chloride.*—(a) *Benzaldehyde* (1 *mol. equiv.*) *added.* A suspension of the phosphine oxide (2) (0.263 g, 0.85 mmol) in deuteriochloroform (1.5 ml) containing acetyl

chloride (0.069 g, 0.88 mmol) and benzaldehyde (0.094 g, 0.89 mmol), was stirred for 4 days at room temperature. A ^{1}H n.m.r. spectrum of the resulting clear solution indicated that acetic acid [δ 2.05 (s)] was the main component. Other signals [with integrated areas with respect to δ_{AcOH} as 100%, given in parentheses] appeared at δ 5.05 (d, J 8.8 Hz; 50%), 2.17 (d; 67%), 2.57 (s; 11%), and 10.1 (s; 50%), corresponding to bis-α-(diphenylphosphinoyl)benzyl ether (5), α-chlorobenzyl acetate (3),[6] acetyl chloride, and benzaldehyde, respectively. No α-acetoxybenzylphosphine oxide (4) was detected.

(b) *Without benzaldehyde.* After 4 days, a suspension of the phosphine oxide (2) (0.235 g, 0.76 mmol) in a solution of acetyl chloride (0.062 g, 0.78 mmol) in deuteriochloroform afforded a clear solution whose ^{1}H n.m.r. spectrum exhibited signals corresponding to acetic acid (δ 2.06; 100%), compounds (4) [δ 1.98 (s) and 6.8 (d); 50%] and (5) [δ 5.05 (d); 45%], acetyl chloride (δ 2.57; 70%), and α-chlorobenzyl acetate (3) [δ 2.17 (s); 20%].[6] [As in (a), the percentages in parentheses refer to the integrated areas of signals relative to δ_{AcOH} as 100%.]

Syntheis of α-Methoxybenzyldiphenylphosphine Oxide (6). —The dimethyl acetal of benzaldehyde (0.96 g, 6.3 mmol) was added to chlorodiphenylphosphine (1.39 g, 6.3 mmol) in a little light petroleum. Within 30 s the mixture had solidified, and it was left under petroleum for several hours. The solid was the phosphine oxide (6), m.p. 172—174° (benzene) (lit.,[11] 169—171°); δ_H (CDCl$_3$) 3.39 (3 H, s) and 5.08 (1 H, d, J 11 Hz); δ_C (CDCl$_3$) 58.51 (d, J 13.7 Hz) and 83.55 (d, J 89 Hz); $\nu_{max.}$ 1 191 and 1 176 cm^{-1} (P=O).

Reaction of the Chloro-ether (10) *with Diphenylphosphine Oxide* (9).—A portion of crude chloro-ether (10) (solid), obtained [5b] by neat reaction of chlorodiphenylphosphine (1a) and benzaldehyde (2 mol. equiv.), was mixed with a solution of diphenylphosphine oxide (9) ($>ca.$ 1 mol. equiv.) and t-butylbenzene (2—3 drops; as internal integration standard) in deuteriochloroform in an n.m.r. tube. The tube was sealed and left at room temperature. N.m.r. spectra recorded at intervals indicated that complete conversion of (10) [δ 6.13 (1 H, d, J 8.5 Hz) and 6.5 (1 H, s)] into bis-α-(diphenylphosphinoyl)benzyl ether (5) [δ 5.05 (2 H, d, J 8.8 Hz)] had occurred in 3 h.

Reaction of Diphenylphosphine Oxide (9) *with Acetyl Chloride.*—To a solution of diphenylphosphine oxide (0.643 g, 3.18 mmol) in deuteriochloroform (1 ml) was added acetyl chloride (0.27 g, 3.46 mmol) in carbon tetrachloride (3 ml). A ^{1}H n.m.r. spectrum taken after 15 min showed signals at δ 11.75 and 2.03 (acetic acid) and 2.6 (acetyl chloride) in the ratio (from methyl signals) 76 : 24. A ^{31}P n.m.r. spectrum taken at the same time confirmed that chlorodiphenylphosphine (1a) (δ_P −80.5 p.p.m. from 85% H$_3$PO$_4$) was the major phosphorus-containing species present. Over the next hour or so, the ratio of the acetyl signals did not change appreciably.

[11] M. Epstein and S. A. Buckler, *Tetrahedron,* 1962, **18**, 1231.