Procedure.—An ether solution of *n*-butylmagnesium bromide was added from a buret to a magnetically stirred ether solution of ketone within 1.2 sec, and the reaction was stopped with acetic acid 1 min after the addition of the reagent. Inverse addition of acetone was conducted with a syringe.

The rate constants, k, of Michael addition of LSH to $CH_2{=}C(R)CO_2CH_3$ were calculated from eq 3. Here the concentration of LSH was determined by an iodometry. The reaction was conducted at various temperatures, and the ΔH^* and the ΔS^* were obtained from Arrhenius plots.[5]

$$LSH + B \overset{K_1}{\rightleftharpoons} LS^- + BH^+$$

$$LS^- + CH_2{=}C(R)CO_2CH_3 \overset{k_2}{\rightleftharpoons} LSCH_2\bar{C}(R)CO_2CH_3$$

$$\frac{-d[LSH]}{dt} = k[LSH][CH_2{=}C(R)CO_2CH_3] \qquad (3)$$

$$k = K_1k_2[B]/[BH^+]$$

Registry No.—I, 625-23-0; II (R = Et), 5582-82-1; *n*-butylmagnesium bromide, 693-03-8; acetone, 67-64-1; methyl ethyl ketone, 78-93-3; CH_3CO *n*-C_3H_7, 107-87-9; CH_3CO *i*-C_3H_7, 563-80-4; CH_3CO *i*-C_4H_9, 108-10-1; laurylmercaptan, 112-55-0; methyl α-methylacrylate, 80-62-6; methyl α-ethylacrylate, 2177-67-5; methyl α-propylacrylate, 3070-66-4; methyl α-isopropylacrylate, 3070-67-5; methyl α-isobutylacrylate, 3070-69-7.

Organophosphorus Chemistry. IV. The Reactions of Trialkyl Phosphites with α-Halo Ketones[1]

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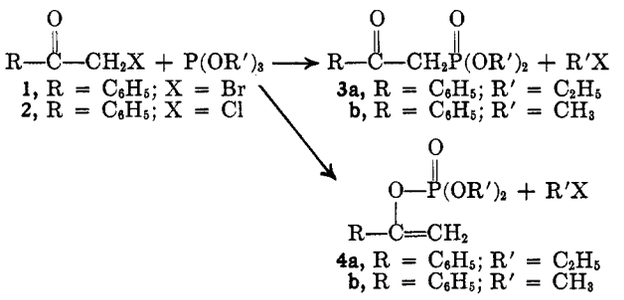
The course of the reactions of certain phenacyl halides and of α-halocyclohexanones with triethyl phosphite, *i.e.*, to form ketophosphonates and/or enol phosphates (Perkow reaction), is not significantly altered by the initial presence of alcohols. Thus, these reactions probably do not proceed *via* initial attack of phosphorus on halogen. Phenacyl bromides give only enol phosphates and no ketophosphonates in reaction with trialkyl phosphites in the presence of acetic acid. A possible mechanism for these reactions is presented and its relationship to the mechanism of the Perkow reaction is discussed. The evidence presented strongly suggests that the Perkow reaction involves initial attack of trialkyl phosphite on carbonyl carbon followed by rearrangement to oxygen.

The reactions of α-halo ketones with trialkyl phosphites lead to ketophosphonates **3** (Arbusov reaction) and enol phosphates **4** (Perkow reaction)[3] (Scheme I).

SCHEME I



We and others have found that the reaction of numerous α-bromo ketones with triphenylphosphine in the presence of methanol, acetic acid, or other prototropic reagents leads to the dehalogenated ketone in high yield.[4,5] These reactions appear to proceed by nucleophilic displacement on bromine by the phosphine assisted by proton transfer to the incipient carbanion. They may also involve a prior protonation or hydrogen-bond formation on the carbonyl oxygen which then makes attack on bromine more feasible. The reactions of α-bromo ketones with triphenylphosphine in anhydrous solvents may also proceed by initial attack on bromine to give enolate bromophosphonium ion pairs which recombine to give either keto- or enol triphenylphosphonium salts and their further reaction products.[5] Ketotriphenylphosphonium salts may also be formed, in some cases at least, by SN2 displacement of bromide ion by triphenylphosphine in aprotic solvents.

Results and Discussion

We now wish to present evidence which indicates that the formation of ketophosphonates most likely occurs by SN2 displacement of halide ion even in the presence of alcohols. Furthermore we have found evidence that enol phosphate formation proceeds most likely by initial attack at carbonyl carbon followed by rearrangement of the phosphorus to carbonyl oxygen[6a] (Scheme II).

2-Bromoacetophenone (**1**) reacts with triethyl phosphite in 1,2-dimethoxyethane ("glyme") or without solvent to give mainly the ketophosphonate **3a** and less of diethyl 1-phenylvinyl phosphate **4a** (Table I). Reaction in the initial presence of ethanol gives a com-

(1) (a) Part of the research was performed at Lehigh University. (b) This investigation was supported in part by Grant No. GP-1354 from the National Science Foundation and AF-AFOSR-938-65 from the Directorate of Chemical Sciences, Air Force Office of Scientific Research. We also acknowledge with thanks the award of funds for a Varian A-60 nmr spectrometer from the National Science Foundation and the award (to M. A.) of the Althouse (1963–1964) and Hornor (1964–1966) Fellowships at Lehigh University.

(2) Address to which correspondence should be sent.

(3) F. W. Lichtenthaler, *Chem. Rev.*, **61**, 607 (1961).

(4) (a) I. J. Borowitz and L. I. Grossman, *Tetrahedron Letters*, 471 (1962); (b) H. Hoffman and H. J. Diehr, *ibid.*, 583 (1962); (c) S. Trippett, *J. Chem. Soc.*, 2337 (1962); (d) P. A. Chopard, R. F. Hudson, and G. Klopman, *ibid.*, 1379 (1965).

(5) (a) I. J. Borowitz and R. Virkhaus, *J. Am. Chem. Soc.*, **85**, 2183 (1963); (b) I. J. Borowitz, K. Kirby, and R. Virkhaus, *J. Org. Chem.*, **31**, 4031 (1966).

(6) (a) A similar pathway for the mechanism of the Perkow reaction has been proposed by P. A. Chopard, V. M. Clark, R. F. Hudson, and A. J. Kirby, *Tetrahedron*, **21**, 1961 (1965). Our work, which had begun before publication of this paper, is mainly based on systems not studied by these authors. (b) This conclusion is supported by current kinetic studies, especially when compared with related studies in the triphenylphosphine–phenacyl bromide system. We also find that the enolate of acetophenone is phosphorylated mainly on oxygen.[7]

(7) S. Firstenberg, research in progress.

SCHEME II

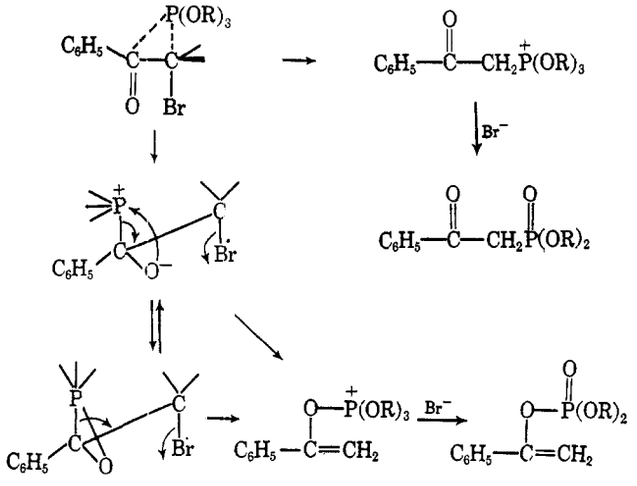


TABLE I

THE REACTIONS OF HALOACETOPHENONES WITH PHOSPHITES

Halo ketone	Reacn condn	Yields, % (or ratios) Keto-phosphonate	Enol phosphate	Ketone	Halo ketone
Bromoacetophenone					
1	*c* (24 hr), *e*, *f*	65	23	1	
1	*d* (20 min), *h*	60	21	0	19
1	*a*, *e*	19	16	30	
1	BuOH, 6 hr, 120°, *e*	42	8	30	
1	$(MeO)_3P$–glyme 87° 24 hr, *f*	52	14	3	0[g]
Chloroacetophenone					
2	*c* (6 hr), *e*	0[g]	85	0[g]	
2	*a*, *e*	0	69	17	
6	*c* (24 hr), *f*	60	0	0	7
7	*c* (24 hr), *h*	62	28	0	10
8	*d* (24 hr), *h*	19	68	0	12.5
8	*b* (23 hr), *h*	10	71.5	3	15

[a] $(EtO)_3P$, excess EtOH, 120° (bath temperature), 6 hr. [b] $(EtO)_3P$, excess EtOH, room temperature. [c] $(EtO)_3P$, in glyme at reflux. [d] $(EtO)_3P$, neat, at room temperature. [e] Products by vpc analysis. [f] Products by nmr ratios on distillate. [g] Trace present by tlc. [g] From nmr ratios on undistilled reaction mixture; ratios, not yields.

plex mixture of products which still contains **3a** and **4a** and some acetophenone **5** (30%). The mixtures were analyzed by gas chromatography and nmr. Similarly the initial presence of ethanol in the reactions of other bromo and chloro ketones with triethyl phosphite does not give dehalogenation as the principal process (Tables I and II). This is in marked contrast to the reactions of bromo ketones with triphenylphosphine as already mentioned. Our results probably eliminate initial attack on halogen by triethyl phosphite for both ketophosphonate and enol phosphate formation from α-halo ketones.[6b]

The simplest and most likely pathway for the formation of **3a** and other ketophosphonates involves the SN2 displacement of halide ion by phosphite. Such displacement is the predominant process in the reactions of **1** with either triethyl or trimethyl phosphite (Table I). As further evidence for the formation of ketophosphonates *via* an SN2 process we find the following ratios of ketophosphonate/enol phosphate (yields in parentheses) in reaction with triethyl phosphite:

TABLE II

THE REACTIONS OF HALOCYCLOHEXANONES WITH TRIETHYL PHOSPHITE

Halo ketone	Reacn condn	Yields, % (or ratios) Keto-phosphonate	Enol phosphate	Ketone	Halo ketone
2-Chlorocyclohexanone					
11	*a*, *c*	0	82	20	
11	*b*, *c*	0	52	2	
2-Bromocyclohexanone, **12**	*a*, *c*	0	49	33	13
	b, *c*	0	73	0	24
2-Chloro-2-methylcyclohexanone, **13**	Neat, 120°, *c*	0	66		
	a, *c*	0	40	32	
2-Bromo-2-methylcyclohexanone, **14**	*a*, *c*	0	70	19	

[a] $(EtO)_3P$, excess EtOH, 120° (bath temperature) 6 hr. [b] $(EtO)_3P$, excess EtOH, room temperature. [c] Products by vpc analysis.

for bromoacetophenone 2.8:1 (88%), for bromopropiophenone 1:4 (87%), for desyl bromide 0:100 (68%), and for bromoisobutyrophenone 0:100 (84%). See the Experimental Section for details. Thus the amount of ketophosphonate regularly decreases with increasing substitution at the carbon–bromine bond as would be expected for an SN2 process.

The reaction of chloroacetophenone **2** with triethyl phosphite gives only the enol phosphate **4a**. The initial presence of ethanol causes only a small amount of dehalogenation as measured by the formation of **5**. The small to moderate yields of ketones in the reactions leading primarily to enol phosphates probably arise from the solvolysis of intermediate enol phosphonium salts, and to a lesser extent, from secondary solvolysis of the enol phosphates. It is found that the relative amount of ketone, as monitored by nmr, slowly increases after a halo ketone triethyl phosphite reaction mixture has been stored for some time. Distillation of such reaction mixtures also increases the amount of ketone present.

Table I also indicates that the ratio of ketophosphonate to enol phosphate decreases for the reactions of bromoacetophenones substituted in the aromatic ring as the electron-withdrawing ability of the substituent group is enhanced; thus the ketophosphonate/enol phosphate ratios are 100% keto for *p*-methoxy-α-bromoacetophenone **6**, 2.8:1 for **1**, 2.2:1 for *m*-methoxy-α-bromoacetophenone **7**, and 1:3.6 for *p*-nitro-α-bromoacetophenone **8**. The electron-withdrawing *m*-methoxy and *p*-nitro groups should enhance attack by phosphite at the carbonyl carbon or oxygen, leading to enol phosphate formation, more than they increase the rate of direct displacement at the ω carbon to give ketophosphonate.[8] The *p*-methoxy group, on the other hand, deactivates the carbonyl and allows attack at the ω carbon to predominate. We believe that the observed effects of aromatic ring substitution are reasonably well explained by the above arguments and that these effects afford additional evidence for the postulated dual pathway leading to the products **3a** and **4a**.

Reaction of **8** with triethyl phosphite in the presence of ethanol gives about the same product ratios as reac-

(8) The reaction of triethyl phosphite with **8** is qualitatively faster than the reaction with **1**.

tion in glyme. Thus attack on bromine of a bromoacetophenone by triethyl phosphite is not observed even when a *p*-nitro substituent is present in the aromatic ring. The presence of this electron-withdrawing group might have stabilized an incipient carbanion **9** resulting from removal of "positive bromine" by phosphite. Alternatively the *p*-nitro substituent would inhibit the formation of a full or partial positive charge on carbonyl carbon so that subsequent dehalogenation *via* attack on bromine on a structure such as **10** would be less likely than in the unsubstituted case (Scheme III).

SCHEME III

REACTIONS WITH 2-HALOCYCLOHEXANONES

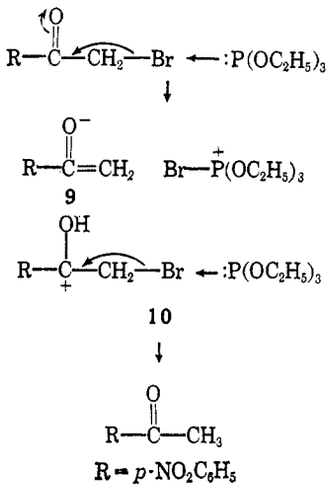
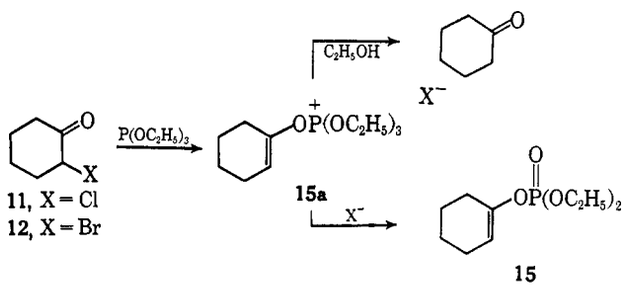


Table II indicates that the reactions of 2-chlorocyclohexanone (**11**), 2-bromocyclohexanone (**12**), 2-methyl-2-chlorocyclohexanone (**13**), and 2-methyl-2-bromocyclohexanone (**14**) with triethyl phosphite in excess ethanol all give mainly the corresponding enol phosphate and no ketophosphonate. The reactions of **11** or **12** with triethyl phosphite are known to give the enol phosphate.[3] Thus, as with the haloacetophenones, the presence of alcohol in these reactions does not appreciably alter the products and does not lead to dehalogenation as the predominant process. Many of these reactions involving halocyclohexanones were originally conducted at *ca.* 120° and did give dehalogenated ketone in appreciable yield. Significantly, reaction of **12** with triethyl phosphite and excess ethanol at room temperature gave the enol phosphate **15** and no cyclohexanone while the same reaction at 120° gave 33% of cyclohexanone. It is reasonable to assume that reaction at the lower temperature gives the enol phosphate which is partially solvolyzed under the conditions of the higher temperature reaction. It is also conceivable that solvolysis of the intermediate enol phosphonium salt **15a** to give cyclohexanone competes somewhat with conversion to **15** at the higher temperature while it does not do so at room temperature[9] (Scheme IV). In any case these reactions indicate that the conversions of **11–14** to the corresponding enol phosphate do not involve attack on halogen.

Effect of Acetic Acid.—The lack of dehalogenation of α-halo ketones by the trialkyl phosphite–alcohol system led us to investigate the effect of a carboxylic acid

(9) This possibility is being further investigated.

SCHEME IV



as a stronger prototropic solvent in these reactions. Reaction of **1** with triethyl or trimethyl phosphite in 4 equiv of acetic acid gave only **4a** and **4b** and no ketophosphonate. Similarly **6** or **8** reacted under these conditions to give the corresponding enol phosphate (Table III). This profound effect of acetic acid on the

TABLE III

REACTIONS OF HALOACETOPHENONES WITH TRIALKYL PHOSPHITES AND ACETIC ACID

		Yields, % (or ratios)			
Halo ketone	Reacn condn	Keto-phos-phonate	Enol phosphate	Ketone	Halo ketone
1	$(EtO)_3P$, room temperature 46 hr, *a*	0	63	4	0
1	$(MeO)_3P$, room temperature 22 hr, *a*	0	77.5	0[b]	0[b]
6	$(EtO)_3P$, room temperature 20 min, *c*	0	63	12	25
8	$(EtO)_3P$, room temperature 24 hr, *c*	0	60	15	20

[a] Products by nmr ratios on distillate. [b] Trace present by tlc. [c] From nmr ratios on undistilled reaction mixture; ratios, not yields. All reactions with excess HOAc present (see the Experimental Section).

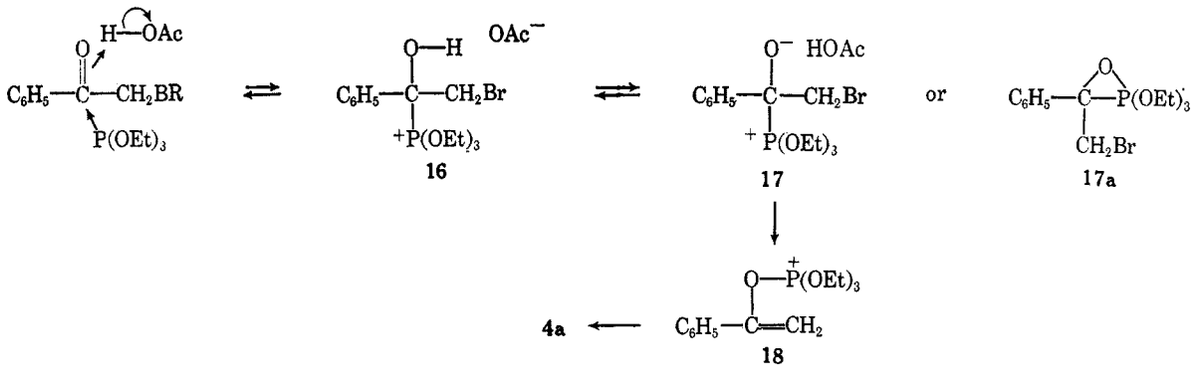
promotion of enol phosphate formation is seen most dramatically in the reaction of **6** which ordinarily gives only ketophosphonate as product. It thus appears that the presence of acids such as acetic acid will be useful in obtaining only enol phosphates from those halo ketones that ordinarily give both ketophosphonates and enol phosphates.

In the presence of acetic acid, attack of trialkyl phosphite at carbonyl carbon of a halo ketone such as **1** is enhanced by protonation at oxygen, and is most likely the major process involved. It is further postulated that the adduct **16** can reversibly lose a proton to give the same dipolar intermediate **17** as results from the addition of phosphite to the halo ketone under aprotic conditions. The intermediate **17** or the phosphorane **17a** then rearranges as already shown to give an enol phosphonium salt **18** which undergoes the well-known Arbusov cleavage to give **4a** (Scheme V).

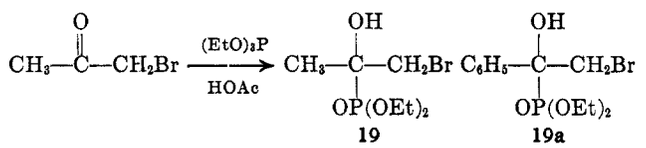
While this sequence may explain the special effect of acetic acid in favoring the formation of **4a** from **1** it also lends supporting evidence to the possibility that formation of **4a** under aprotic conditions also results from the intermediacy of **17**.[6a] Thus the protic and aprotic formation of enol phosphates may occur *via* attack of phosphite on carbonyl carbon in its protonated and normal forms, respectively.

Further work will determine the generality of the "carboxylic acid effect" in promoting the formation of enol phosphates. Some recent observations of Hud-

SCHEME V



son, Clarke, *et al.*, are of interest in this respect.[6a] These investigators found that, while bromoacetone reacted with trimethyl phosphite in a large excess of acetic acid to give α-hydroxyphosphonate **19**, reaction with less acetic acid present favored the formation of enol phosphate.

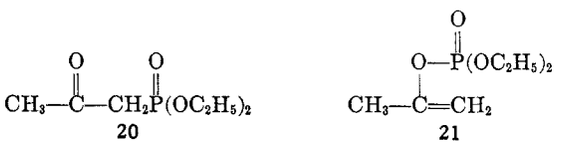


While a direct comparison of concentrations is not possible owing to insufficient data, it appears that in concentrated solution bromoacetone behaves similarly to the bromoacetophenones that we have investigated; *i.e.*, enol phosphate is formed. We have not found any α-hydroxyphosphonate in our reactions. We have not yet attempted our reactions in the presence of a large excess of acetic acid.

It may be that the concentration effect can be explained as follows. In concentrated solution, as pertains to our reactions, the equilibrium between the protonated form **16** and the dipolar species **17** allows rearrangement of **17** to **18**. In the presence of a large excess of acetic acid this equilibrium lies much more toward **16** and a new reaction becomes predominant, *i.e.*, the Arbusov cleavage of ethoxyl by acetate ion to give **19a**. We have not yet observed **19a**, however.

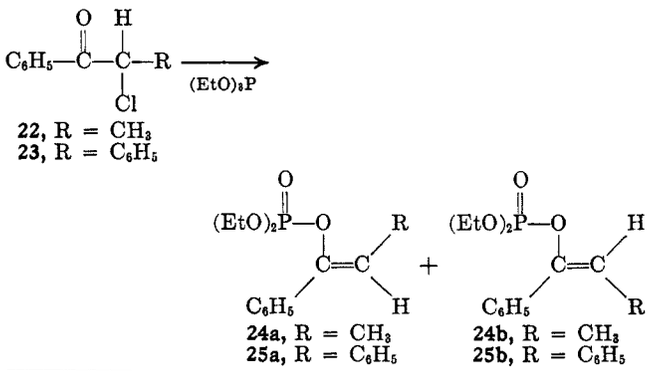
In order to ensure that the effect of acetic acid was not due to products derived from trialkyl phosphite and acetic acid, the following control experiments were performed. Reaction of triethyl phosphite with acetic acid at room temperature gave diethyl phosphite (40%).[10] The conditions were approximately those under which the halo ketone reactions were performed. However, there was no reaction of bromoacetophenone with diethyl phosphite in acetic acid after 29 hr.[11] Thus even if some diethyl phosphite were formed in the bromoacetophenone–triethyl phosphite–acetic acid reactions, it should not interfere with the more reactive triethyl phosphite. The lower nucleophilicity of dialkyl phosphites in comparison with trialkyl phosphites is well known.[12] Actually there is doubt as to whether any triethyl phosphite is converted to diethyl phosphite in our bromoacetophenone reactions since (a) the bromoacetophenone–triethyl phosphite reactions appear to be faster than the acetic acid–triethyl phosphite reaction and (b) the high material balance of the bromoacetophenone reactions (Table III) indicates availability of most, if not all, of the trialkyl phosphite for reaction with the bromoacetophenones.

Since it is known that the ketophosphonate **20** is rearranged to the enol phosphate **21** in the presence of



phosphoric acid,[13] the possibility of the conversion of **3a** to **4a** with acetic acid was investigated. Treatment of a mixture of **3a** and **4a** with a small amount of acetic acid, either at room temperature or at 110°, resulted in a small increase in the relative amount of **4a**. Thus the rearrangement of **3a** to **4a** under our reaction conditions should occur to only a minor extent if at all.

Reactions with Other Halo Ketones.—α-Chloropropiophenone **22** and desyl chloride **23** each react with triethyl phosphite to give mixtures of *cis*- and *trans*-vinyl phosphates. No ketophosphonate is found in these reactions upon nmr examination. Studies on the stereochemistry of vinyl phosphate formation in such cases are in progress.[7] It is concluded that with α-chloro ketones displacement of chloride ion is too slow to compete with vinyl phosphate formation.



(10) The conversion of trialkyl phosphites to dialkyl phosphites with acids is well known; *cf.* B. Iselin, W. Rittel, P. Sieber, and R. Schwyzer, *Helv. Chim. Acta*, **42**, 373 (1957).

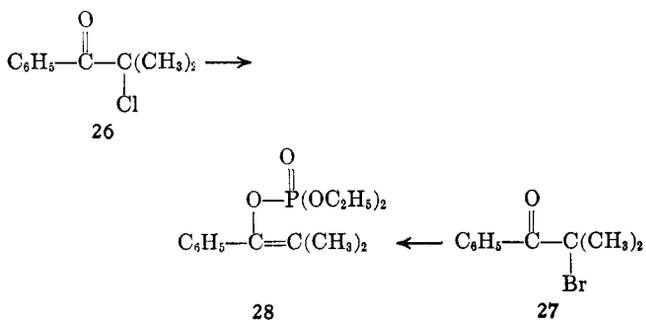
(11) In contrast, the reaction of **2** with diethyl phosphite under aprotic conditions is reported to give the hydroxyphosphonate resulting from addition across the carbonyl; *cf.* B. A. Arbusov, "Phosphoric Esters and Related Compounds," Special Publication No. 8, The Chemical Society, London, 1957, p 51.

(12) R. F. Hudson, "Structure and Mechanism in Organophosphorus Chemistry," Academic Press Inc., New York, N. Y., 1965, p 124.

(13) H. Machleidt and G. U. Strehlke, *Angew. Chem. Intern. Ed. Engl.*, **3**, 443 (1964).

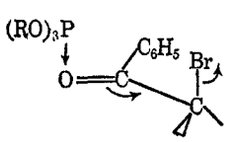
All of the above data do not allow a firm decision to be made as to whether the initial site of attack in the Perkow reaction is at carbonyl carbon or oxygen, although attack at carbon is suggested. This possibility is greatly enforced by the following facts.

Chloro- and bromocyclohexanone react at about the same rate in competition for 1 equiv of triethyl phosphite to give **15**. The reaction was followed by vpc to 57% of completion; see the Experimental Section for details. Furthermore chloroisobutyrophenone **26** reacts faster than does bromoisobutyrophenone **27** in a similar competition experiment to give the enol phosphate **28**. This experiment was followed by nmr and



was conducted at 34.9°. The relative reactivities of the haloisobutyrophenones are confirmed by separate kinetic measurements for **26** and **27** each in reaction with triethyl phosphite. These measurements are now in progress and will be published elsewhere.[7]

We conclude that at least in the Perkow reactions cited above the rate-determining step in enol phosphate formation cannot involve the loss of halide ion since bromide ion should then leave much more rapidly than does chloride ion.[14] Therefore the SN2′ mechanism involving initial attack on oxygen with concomittant loss of halide ion is unreasonable.[15]



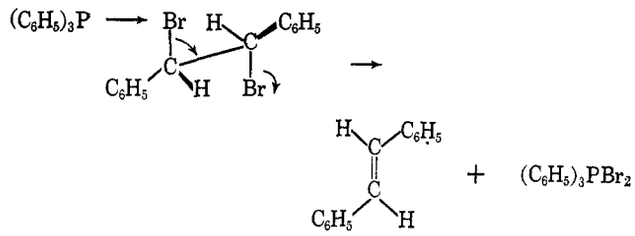
Our results are best explained by a rate-determining addition of phosphite to carbonyl carbon followed by rapid rearrangement to oxygen and loss of halide ion after the rate-limiting step. Such addition to carbonyl carbon might be expected to be somewhat faster for an α-chloro ketone than for an α-bromo ketone owing to the greater inductive effect of the chlorine group. A related argument has been recently given by Miller with reference to the reactions of trihalomethylcyclohexadienones with phosphites to explain the opposite result.[16]

(14) Although there are apparently no data on SN2′ reactions involving phosphorus nucleophiles, the SN2 reactions of di-*n*-butyl phosphite or tributyl phosphine go faster with propyl bromide than with propyl chloride by factors of 246:1 and 125:1, respectively. See ref 12.

(15) (a) A nonconcerted rate-determining attack on carbonyl oxygen followed by rapid loss of halide ion is admissible but not likely since it would involve the formation of a carbanion stabilized at best by phenyl. The alternate attack on carbonyl carbon places the negative charge on oxygen and is a more reasonable possibility. (b) Implicit in our discussion is the assumption that the final step which involves the conversion of an enol phosphonium salt to an enol phosphate is not rate determining. This assumption is at this point by analogy to the kinetics of the reaction of ethyl iodide with triethyl phosphite as reported by G. Aksnes and D. Aksnes, *Acta. Chem. Scand.*, **18**, 38 (1964). Whether it is valid in our systems will be determined.

(16) B. Miller, *J. Am. Chem. Soc.*, **88**, 1841 (1966).

We further conclude that triphenylphosphine is much more reactive than is triethyl phosphite toward "positive halogen" as in halo ketones. It also appears that triethyl phosphite is more reactive toward carbonyl groups than is triphenylphosphine. We have found the following reactivity difference in the 1,2-debromination of *meso*-stilbene dibromide with trivalent phosphorus species. While triphenylphosphine gives stilbene (99%) and triphenylphosphine dibromide (isolated as triphenylphosphine oxide in 95% yield), triethyl phosphite gives no reaction under the same conditions.[17] This elimination most likely involves attack on bromine.



We have also found that triethyl phosphite is much more reactive than is triphenylphosphine in reactions with fluorenone which involve phosphorus–oxygen bond formation.[18] These results and their interpretation will be discussed in separate publications. Our data lend support to the view that triphenylphosphine is a "softer nucleophile" than is triethyl phosphite so that the former reacts on "soft" bromine while the latter reacts preferentially at the "harder" carbonyl group.[19] Further research on the relative "halophilicities" (nucleophilities toward halogen) of trivalent phosphorus species and on the reactions of α-halocarbonyl compounds with tertiary phosphites including kinetic studies is in progress.

Experimental Section[20]

Reaction of Bromoacetophenone with Triethyl Phosphite. A. In 1,2-Dimethoxyethane.—A solution of bromoacetophenone (3.98 g, 0.020 mole) in 1,2-dimethoxyethane (4 ml) was added dropwise with stirring to triethyl phosphite (3.32 g, 0.020 mole) at 120°, and the resultant mixture was refluxed for 24 hr. After the solvent was removed *in vacuo* the residual liquid was distilled to give a mixture of **3a** and **4a** (4.50 g, 88%), bp 100–140° (0.15 mm). The mixture consisted of *ca.* 74:26 **3a** to **4a** and *ca.* one part of acetophenone (as determined by nmr) or yields of 65% **3a**, 23% **4a**, and 1% acetophenone. Analysis by tlc and vpc revealed the same components (vpc ratio of **3a**/**4a** was 70:3)). The nmr ratios were used as a better indication of the actual product ratios rather than the vpc ratios which were merely relative areas and could not be fitted to calibration curves owing to the lack of pure **3a**. The mixture of **3a** and **4a** exhibited infrared peaks ($CHCl_3$) at 5.95 (carbonyl) and 6.10 μ (double

(17) D. Weiss and M. Thames, unpublished results.

(18) M. Anschel, results to be published. See also A. C. Poshkus and J. E. Herweh, *J. Org. Chem.*, **29**, 2567 (1964).

(19) *Cf.* ref 12, p 116.

(20) Microanalyses were performed by Professor V. B. Fish of the Department of Chemistry, Lehigh University, and by Galbraith Laboratories, Knoxville, Tenn. Infrared spectra were recorded on a Beckman IR-8 infrared spectrophotometer. Nmr spectra were recorded on a Varian A-60 spectrometer with TMS as an internal standard. Boiling points are uncorrected. Gas chromatograms were recorded on a Varian Aerograph A-700 gas chromatograph. The best results were obtained with glass columns packed with 3–5% SE-30 on Chromosorb W although Carbowax 20 M columns were also used. Peak areas were obtained by triangulation or by cutting out the paper under the peak and weighing it. Calibration curves were used whenever feasible. The accuracy of yields as so determined is estimated to be to 3–5%. Triethyl phosphite was dried and distilled from calcium hydride, bp 156–157°. Thin layer chromatography was performed on Brinkman silica gel HF_{254} using mainly 5% ethyl acetate–benzene as the developing solution.

bond of **4a**). The nmr spectrum ($CDCl_3$) of the mixture exhibited a doublet centered at τ 6.4 ($J_{P^{31}H}$ = 22.5 cps) for the methylene of **3a**, a multiplet centered at 4.75 for the olefinic protons of **4a**, and the following peaks common to **3a** and **4a**: 5 H multiplets centered at 2.0 and 2.5 (aromatic protons), a 4 H doublet of quartets centered at 5.95 (J = 7 cps, methylene of ethyl), and a 6 H doublet of triplets centered at 8.80 (J = 7 cps, methyl of ethyl).

B. In Ethanol or Butanol.—A solution of bromoacetophenone (3.98 g, 0.020 mole) in absolute ethanol (5 ml) was added dropwise to triethyl phosphite (3.32 g, 0.020 mole) with stirring at *ca.* 120° (bath temperature) and the mixture was refluxed for 6 hr. Analysis of the resultant mixture by vpc (by relative peak area comparison and the use of a calibration curve for **4b**) gave results shown in Table I. Reaction in butanol was similarly done at a bath temperature of 135°.

C. No Solvent.—Triethyl phosphite (3.32 g, 0.020 mole) was added dropwise to bromoacetophenone (3.98 g, 0.020 mole) and the mixture was kept at room temperature with stirring. After 20 min an aliquot was examined by nmr and found to be **3a** (60%), **4a** (21%), and unreacted **1** (19%). The numbers are nmr ratios and should be reasonably related to the actual yields since no extraneous peaks were observed and the loss of material was minimal.

D. In Acetic Acid.—A solution of **1** (3.98 g, 0.020 mole) in acetic acid (4.80 g, 0.080 mole) was added dropwise with stirring to triethyl phosphite (3.32 g, 0.020 mole) and was kept at room temperature for 46 hr. After removal of acetic acid and unreacted phosphite *in vacuo* the residual liquid was distilled to give 3.30 g, bp 115–122° (0.15 mm) of a liquid; nmr ($CDCl_3$) indicated enol phosphate **4a** and acetophenone **5** in 97:3 ratio or yields of 63% **4a** and 4% **5**. Examination of the liquid by tlc gave only these two components.

Reaction of Bromoacetophenone with Trimethyl Phosphite. A. In 1,2-Dimethoxyethane.—Reaction of **1** (0.020 mole) in 1,2-dimethoxyethane (4 ml) with trimethyl phosphite (2.48 g, 0.020 mole) at 87° for 24 hr as in section A above gave 3.11 g of distilled liquid, bp 110–142° (0.15 mm). Examination of the liquid (tlc, nmr) indicated the presence of **3b** and **4b** in 3.7:1 ratio or yields of 52% **3b** and 14% **4b**; a 3% yield of unreacted **1** was also found.

B. In Acetic Acid.—Reaction of **1** (0.020 mole) with trimethyl phosphite as in section D above gave 3.54 g, bp 140–144° (0.6–0.8 mm), of a liquid; nmr revealed it to be only **4b** (77.5%). Traces of **1** and **5** were found by tlc.

Reaction of Chloroacetophenone with Triethyl Phosphite. A. No Solvent.—Chloroacetophenone (3.09 g, 0.020 mole) was added to triethyl phosphite (3.3 g, 0.020 mole) at 120° (bath temperature) and the mixture was refluxed for 6 hr. Distillation gave **4a** (4.35 g, 0.0169 mole, 85%), bp 110–118° (0.15 mm), pure by nmr and vpc analysis, although tlc showed the presence of a trace of **3a** and of **5**.

B. In Ethanol.—Chloroacetophenone (3.09 g, 0.020 mole) in absolute ethanol (5 ml) was added dropwise to triethyl phosphite (3.32 g, 0.020 mole) at 120° (bath temperature), and the mixture was refluxed for 6 hr. Distillation gave a forerun (3.37 g) which contained 8.5% of **5** (vpc) and a main fraction, bp 80–161° (3.5–5.0 mm), of 5.015 g which contained 2.5% **5** and 70.5% **4a**; actual yields of **5** (0.41 g, 0.0034 mole, 17%) and **4a** (3.52 g, 0.0138 mole, 69%) were thus calculated.

Reaction of *p*-Nitro-α-bromoacetophenone with Triethyl Phosphite. A. No Solvent.—Triethyl phosphite (3.32 g, 0.020 mole) was added at once to **8** (4.88 g, 0.020 mole) to give an exothermic reaction during which **8** went into solution. The resulting solution was cooled to room temperature and so kept for 23 hr. Analysis by nmr revealed the presence of **8**, the ketophosphonate **3a** (R = *p*-$NO_2C_6H_5$), and the enol phosphate **4a** (R = *p*-$NO_2C_6H_5$) in a ratio of 1:1.53:5.47. Assuming that these were the only products, as detected by nmr at least, the ratio given corresponds to yields of 0.0025 mole (12.5%) of unreacted **8**, 0.0038 mole (19%) of ketophosphonate, and 0.0137 mole (68%) of enol phosphate. A trace of *p*-nitroacetophenone was found by tlc but was not detected by nmr. This ratio was based on the integrated areas of the methylene protons for the products which absorbed as a singlet at τ 5.15 for **8**, a doublet ($J_{P^{31}H}$ = 18 cps) centered at 6.20 for the ketophosphonate, and a doublet of triplets ($J_{P^{31}H}$ = 2 cps) at 4.30 and 4.55 for the enol phosphate. As a check the total integrated area of the three different methylenes was found to be exactly 0.5 that of the 4 H aromatic proton area.

B. In Ethanol or Acetic Acid.—Triethyl phosphite was added dropwise to **8** (amounts as above) in either ethanol (6 ml) or acetic acid (4.80 g, 0.080 mole) at room temperature. After 24 hr the solvent and unreacted phosphite were removed *in vacuo* and the residual solution was examined by nmr as above. *p*-Nitroacetophenone was estimated in these reaction *via* its singlet methyl group at τ 7.32. Qualitative results by tlc were in agreement with the nmr data.

Reaction of *p*-Methoxy-α-bromoacetophenone with Triethyl Phosphite. A. In 1,2-Dimethoxyethane.—Reaction of triethyl phosphite (1.66 g, 0.010 mole) with **6** (2.29 g, 0.010 mole) in 1,2-dimethoxyethane (5 ml) at reflux for 24 hr followed by removal of volatile material *in vacuo* left 2.35 g of a liquid which was mainly **6** and ketophosphonate by nmr. Distillation gave 1.89 g, bp 168–172° (0.05 mm), of a liquid which was indicated by nmr to be 91:9 ketophosphonate **3a** (R = *p*-$MeOC_6H_5$) and unreacted **6**. A trace of the corresponding enol phosphate was found by tlc.

Anal. Calcd for $C_9H_9BrO_2$: Br, 34.93. Found: 3.11. (This corresponds to 8.9% **6** in the above liquid in excellent agreement with the nmr data.)

On the basis of the above ratio, the yields of distilled products are 0.0060 mole (60%) of ketophosphonate (75% maximum before distillation) and 0.00074 mole (7.4%) of **6** (9% maximum before distillation).

B. In Acetic Acid.—Reaction of triethyl phosphite and **6** (0.010 mole each) in acetic acid (2.40 g, 0.040 mole) for 20 min gave, by nmr analysis on an aliquot, a mixture of the enol phosphate **4a** (R = *p*-$MeOC_6H_5$, 63%), **6** (25%), and *p*-methoxyacetophenone (12%). No other compounds were present. After 1 hr the mixture had turned a dark brown and was not further examined.

Reaction of *m*-Methoxy-α-bromoacetophenone with Triethyl Phosphite.—Triethyl phosphite (3.23 g, 0.020 mole) was added dropwise to a solution of **7** (4.58 g, 0.020 mole) in 1,2-dimethoxyethane (5 ml) at reflux temperature. After 24 hr at reflux the solution was concentrated *in vacuo* and an aliquot was removed for nmr analysis. A mixture of ketophosphonate **3a** (R = *m*-$MeOC_6H_5$, 62%), enol phosphate **4a** (R = *m*-$MeOC_6H_5$, 28%), and **7** (10%) was indicated. Distillation gave 3.66 g, bp 175–185° (0.75 mm), of ketophosphonate, enol phosphate, **7**, and *m*-methoxyacetophenone in the ratio 54:34:7:5. The corresponding yields were ketophosphonate (33%), enol phosphate (21%), **7** (6%), and *m*-methoxyacetophenone (6%).

Reaction of 2-Chlorocyclohexanone with Triethyl Phosphite.—A solution of **11** (2.64 g, 0.020 mole) in absolute ethanol (5 ml) was added dropwise to triethyl phosphite (3.32 g, 0.020 mole) and the resultant solution was refluxed for 6 hr. Analysis by vpc indicated enol phosphate **15** (82%) and cyclohexanone (20%). A genuine sample of **15**, used to establish a vpc calibration curve, was obtained from the known reaction of **11** with triethyl phosphite.[21] Similar reaction at room temperature for 4 hr gave **15** (52%) and cyclohexanone (2%). Although the yield of **15** varied considerably in repetitions of the room temperature reaction, the yield of cyclohexanone was always small.

Reaction of 2-Bromocyclohexanone with Triethyl Phosphite.—A solution of **12** (3.54 g, 0.020 mole) in absolute ethanol (5 ml) was added dropwise to triethyl phosphite (3.32 g, 0.020 mole) and the resultant solution was refluxed for 6 hr. After removal of the solvent *in vacuo*, the residual liquid was distilled to give (1) 4.34 g, bp 37–38° (0.6 mm), and (2) 3.98 g, bp 108–109° (0.2 mm). Analysis by vpc indicated enol phosphate (49%), cyclohexanone (33%), and **12** (13%). A similar experiment performed at room temperature for 6 hr indicated enol phosphate (73%) and **12** (24%).

Reaction of 13 and 14 with Triethyl Phosphite. A. Reaction of 13 (Neat).—Addition of **13**[22] (2.13 g, 0.0146 mole) dropwise to triethyl phosphite (2.42 g, 0.0146 mole) at a bath temperature of 120° followed by heating at 120° for 6 hr gave 2.40 g of 2-methylcyclohexenyl diethyl phosphate (0.0096 mole, 66%), bp 91–92° (0.1 mm). The nmr spectrum (CCl_4) of **29** exhibited a 3 H doublet at τ 8.37 ($J_{P^{31}H}$ = 1.5 cps) for the olefinic methyl and peaks for alicyclic and ethyl group protons.

B. Reactions of 13 and 14[23] in Ethanol.—Reaction of either **13** or **14** and triethyl phosphite (0.020 mole each) in absolute

(21) Kindly provided by Professor G. Stork.

(22) E. W. Warnhoff and W. S. Johnson, *J. Am. Chem. Soc.*, **75**, 494 (1953).

(23) Prepared in 58% yield by the bromination of 2-methylcyclohexanone in carbon tetrachloride containing a small amount of acetic acid, bp 43–45° (0.15 mm).

ethanol (5 ml) followed by a 6-hr reflux period gave mixtures which were analyzed by vpc. See Table II for results.

Treatment of 3a and 4a with Acetic Acid.—A mixture of 76.3:23.7 **3a** and **4a** was placed in an nmr tube under nitrogen and acetic acid (3 drops) was added. After 6 hr at room temperature the ratio was 70.8:29.2. No further change occurred after 24 hr. The mixture was heated with an additional 0.8 ml of acetic acid for 4 hr to give no further change in the ratio of **3a** and **4a**. Some **5** was formed, however.

Reaction of 12 and 11 in Competition with Triethyl Phosphite.—A mixture of **12** and **11** (0.020 mole each) in 1,2-dimethoxyethane (5 ml) was added dropwise to triethyl phosphite (3.32 g, 0.020 mole) at a bath temperature of 85° with stirring. Aliquots were taken at intervals of 1, 2, 3.3, and 4.5 hr and analyzed by vpc to show remaining **12** and **11** in ratios of 1:1, 1.06:1, 1.12:1, and 1.05:1. Known mixtures of **12** and **11** were similarly analyzed to an accuracy of ±5%. After 4.5 hr the reaction had proceeded to give 57% **15**, as determined with a calibration curve for **15**. No other products were found.

Reaction of Triethyl Phosphite with Acetic Acid.—Triethyl phosphite (3.32 g, 0.020 mole) was treated with acetic acid (4.80 g, 0.080 mole) at room temperature for 25 hr to give diethyl phosphite (40% by vpc analysis using a calibration curve made with genuine diethyl phosphite) and starting compounds.

Attempted Reaction of 1 with Diethyl Phosphite.—Treatment of **1** (2.63 g, 0.0132 mole) with diethyl phosphite (1.82 g, 0.0132 mole) in acetic acid (0.053 mole) at room temperature for 28.8 hr led to no reaction as indicated by nmr examination.

Reaction of Bromopropiophenone with Triethyl Phosphite.—A mixture of α-bromopropiophenone (4.26 g, 0.020 mole) and triethyl phosphite (4.15 g, 0.025 mole) was stirred at 100° (bath temperature) for 24 hr and distilled to give 4.69 g (87% yield), bp 115–119° (0.25 mm), of a mixture of two isomeric enol phosphates **24** and O,O-dimethyl α-methylbenzoylmethyl phosphonate **30** in a ratio of 3:1:1. The product ratio was determined from the nmr spectrum ($CDCl_3$) which exhibited a 0.39 H multiplet at τ 1.8–2.1 (*ortho*-aromatic H of **30**), 4.6 H multiplet at 2.4–2.9 (all other aromatic H), 0.8 H doublet of quartets further split by P^{31} at 4.1–4.45 (vinyl H of **24a** and **24b**), 4.2 H doublet of quartets centered at 5.92 (J_{HH} = 7 cps, $J_{P^{31}H}$ = 1.5 cps, 4 H of CH_2 of ethyl group and superimposed 0.2 H methine proton of **30**), 1.8 H doublet of doublets centered at 8.16 (J_{HH} = 7 cps, $J_{P^{31}H}$ = 3 cps, vinyl methyl of **24a** or **24b**), 1.2 H irregular quintet centered at 8.4 (0.6 H each of vinyl methyl of **24b** or **24a** and methyl of **30**), and a 6 H doublet of triplets centered at 8.85 (J_{HH} = 7 cps, $J_{P^{31}H}$ = 1 cps, CH_3 of ethyl group). Another sample, enriched in **30**, showed an nmr (CCl_4) doublet centered at 8.43 (J_{HH} = 7 cps) for the methyl group of **30**.

Reaction of Chloropropiophenone 22 with Triethyl Phosphite.—Reaction of **22** (3.36 g, 0.020 mole) and triethyl phosphite (0.025 mole) under similar conditions to the above experiment gave 4.7 g (0.0174 mole), bp 115–117° (0.2 mm), an 87% yield of the enol phosphates **24a** and **24b**. The nmr spectrum ($CDCl_3$) exhibited a 5 H multiplet centered at τ 2.66 (aromatic H), a 1 H multiplet at 4.05–4.6 (vinyl H), a 4 H doublet of quartets centered at 5.95 (CH_2 of ethyl), a 3 H doublet of doublets of doublets with two lines superimposed (a total of seven lines) at 8.05–8.42 (J_{HH} = 7 cps, $J_{P^{31}H}$ = 2.5 cps; vinyl methyls of **24a** and **24b**), and a 6 H doublet of triplets centered at 8.8 (CH_3 of ethyl; splittings for ethyl group protons as in the previous experiment). The differentiation of **24a** and **24b** awaits our further experimentation. The mixture was redistilled twice for analysis.

Anal. Calcd for $C_{13}H_{19}O_4P$: C, 57.77; H, 7.09. Found: C, 57.53; H, 7.15.

Reaction of Bromoisobutyrophenone 27 with Triethyl Phosphite.—Reaction of **27** (4.54 g. 0.020 mole) with triethyl phosphite (3.35 g, 0.020 mole) at 100° (bath temperature) for 48 hr followed by distillation gave the enol phosphate **28** (4.95 g, 0.0168 mole, 84%), bp 115–17° (0.2 mm), with one peak on vpc.

Reaction of Chloroisobutyrophenone 26 with Triethyl Phosphite.—Reaction of **26**[24] (3.64 g, 0.020 mole) with triethyl phosphite (0.020 mole) as above but for 16 hr gave **28** (3.55 g, 0.0125 mole, 63%): bp 126–128° (0.3 mm); infrared (neat) at 1680 cm^{-1}; nmr (neat) gave a 5 H singlet at τ 2.62 (aromatic), 4 H quintet centered at 6.10 ($J \cong 7$ cps, CH_2 of ethyl group), 3 H doublets centered at 8.13 and 8.36 ($J_{P^{31}H}$ = 2.5, 3.5 cps, vinyl methyls), and a 6 H triplet centered at 8.95 (J = 7 cps, CH_3 of ethyl).

Anal. Calcd for $C_{14}H_{21}O_4P$: C, 59.14; H, 7.45; P, 10.89. Found: C, 59.34; H, 7.60; P, 10.76.

Reaction of Desyl Bromide and Desyl Chloride with Triethyl Phosphite.—Desyl Bromide **31** (5.50 g, 0.0207 mole) was added to triethyl phosphite (3.35 g, 0.020 mole) and the resultant mixture was heated at 100° (bath temperature) for 16 hr. Distillation gave 1,2-diphenylvinyl diethyl phosphate **25** (4.60 g, 0.0141 mole, 68% yield), bp 179–180° (0.25 mm). The nmr spectrum (CCl_4) gave a vinyl proton doublet at τ 3.65 ($J_{P^{31}H}$ = 1 cps) and peaks for aromatic and ethyl group protons.

Desyl Chloride **23** (4.60 g, 0.020 mole) similarly reacted with triethyl phosphite (4.15 g, 0.025 mole) to give a 2:1 mixture of the isomers of **25** (4.65 g, 70.5% yield), bp 158–160° (0.13 mm). A more detailed analysis of the isomers of **25** will follow in another publication.

Reaction of 26 and 27 in Competition for Triethyl Phosphite.—To a mixture of chloroisobutyrophenone **26** (4.666 g, 0.02500 mole) and bromoisobutyrophenone **27** (5.678 g, 0.02500 mole) in a flask was added triethyl phosphite (4.292 g, 0.02584 mole) under a slow nitrogen stream. The sample was sealed and mixed. An aliquot was removed by syringe through a rubber-capped side arm and rapidly placed in an nmr tube which was then closed with a tight-fitting cap. The tube was kept in a constant-temperature bath at 34.9°. A determination by nmr at "zero time" gave a ratio of **27**/**26** of 1.03. The ratio of **27**/**26** increased with time as the vinyl phosphate **28** was formed to reach a steady value of 1.95 after 42.5 hr (reaction about 70–80% complete). Several other runs (at 35 or 100°) gave similar results. The ratio of **27** to **26** was determined from the integrated nmr areas of the singlet methyl peaks for **26** and **27** which were at τ 8.22 and 8.08, respectively. The methyls of the product enol phosphate **28** did not overlap with those of **26** and **27**. Better separation of these various methyl peaks was obtained in benzene solution which also gave a result indicating a more rapid disappearance of the chloro ketone than the bromo ketone. In either benzene solution or neat the methyl groups of the chloro ketone absorbed at higher field than did the bromo ketone.

Registry No.—**1**, 70-11-1; triethyl phosphite, 122-52-1; **2**, 532-27-4; **3a**, 3453-00-7; **3b**, 1015-28-7; **4a**, 1021-45-0; **4b**, 4202-12-4; trimethyl phosphite, 121-45-9; **6**, 2632-13-5; **7**, 5000-65-7; **8**, 99-81-0; **11**, 822-87-7; **12**, 822-85-5; **13**, 10409-46-8; bromopropiophenone, 2114-00-3; **22**, 6084-17-9; **23**, 447-31-4; **24b**, 10409-51-5; **26**, 7473-99-6; **27**, 10409-54-8; **28**, 10409-55-9; **30**, 10409-56-0; **31**, 1484-50-0.

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(24) D. Wyman and P. Kaufman, *J. Org. Chem.*, **29**, 1956 (1959).