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THE MECHANISM OF THE REACTION BETWEEN TRIALKYL PHOSPHITES AND α-HALOGENATED KETONES*

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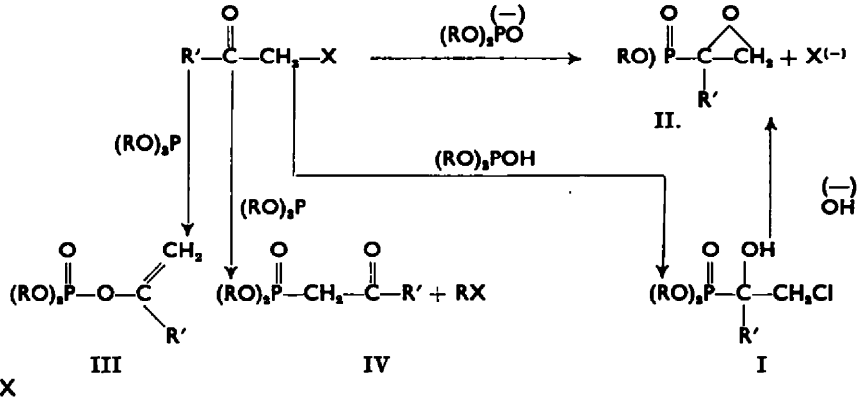
THE reactions between α-halogenated ketones and phosphites are extremely complex and a variety of products have been reported.[1] Thus dialkyl phosphites normally react at the carbonyl group to give α-hydroxy (I) and epoxy (II) phosphonate esters,[2] in line with the tendency of other highly basic nucleophiles, e.g. $OR^{(-)}$, $OH^{(-)}$, RNH_2, to react preferentially at the carbonyl carbon atom[3].



On the other hand trialkyl phosphites (and also dialkylphosphonites and alkylphosphinites) normally give enol phosphates (III) according to the Perkow reaction, together with varying amounts of β-ketophosphonates (IV) by the alternative Arbusov reaction.[4] Tertiary phosphines give similar products, but whereas triethyl phosphite gives mainly enol esters with α-chloroketones and phosphonate esters with α-bromoketones, triphenylphosphine gives phosphonium salts with α-chloroketones and quasi-phosphonium salts with α-bromoketones.[5]

* The Perkow reaction

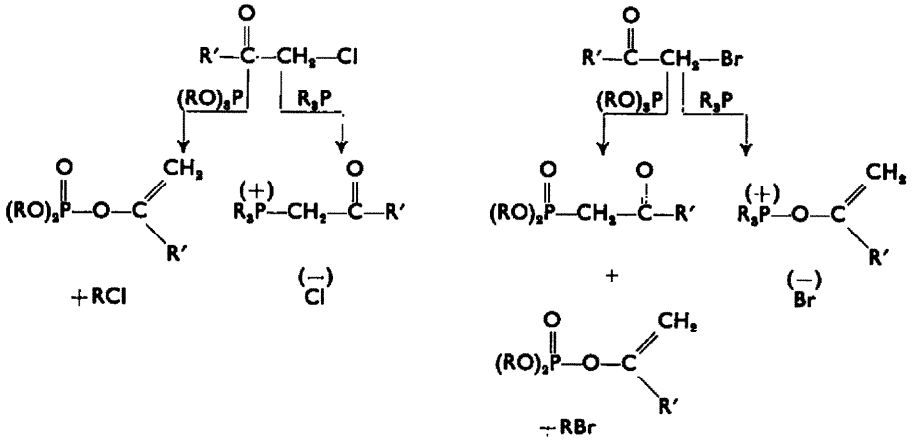
[1] F. W. Lichtenthaler, *Chem. Rev.* **61**, 607 (1961).

[2] V. S. Abramov and A. S. Kapustina, *Zh. Obsh. Khim.* **27**, 1012 (1957); *Chem. Abstr.* **52**, 3667 (1958); A. N. Pudovik and L. G. Biktimirova, *Zh. Obsh. Khim.* **27**, 1708 (1957); *Chem. Abstr.* **52**, 3714 (1958).

[3] B. A. Arbuzov, V. S. Vinogradova and N. A. Polezhaeva, *Dokl. Akad. Nauk SSSR* **121**, 641 (1958); *Chem. Abstr.* **53**, 1180 (1959).

[4a] W. Perkow, K. Ullerich and F. Meyer, *Naturwiss.* **39**, 353 (1952);
[4b] J. F. Allen and O. H. Johnson, *J. Amer. Chem. Soc.* **77**, 2871 (1955).

[5] H. Hoffmann and H. J. Diehr, *Tetrahedron Letters* 583 (1962); I. J. Borowitz and R. Virkhaus, *J. Amer. Chem. Soc.* **85**, 2183 (1963).



It is evident, therefore, that changes in the structure of the phosphorus compound and haloketone produce profound changes in the product composition. The Perkow reaction has been widely investigated in recent years and the following generalizations have resulted (see the review by Lichtenthaler[1]).

(1) At least one aliphatic alkoxy group is necessary for reaction. Thus triaryl phosphites are unreactive towards chloral whereas monoalkyl diaryl phosphites yield enol phosphates readily[4b] indicating that electronic release from the alkoxy group strongly assists the elimination of the halide ion.

(2) The reactivity of various carbonyl compounds increases with the affinity of nucleophiles for the carbonyl group. Thus aldehydes react more readily than ketones,

TABLE 1. RATIOS OF ENOL PHOSPHATE TO PHOSPHONATE PRODUCED (TOTAL ISOLATED YIELDS 60–70%)

	Chloroacetone	Bromoacetone	Iodoacetone
At ca. 150°	90:10	20:80	
Refluxing ether		80:20	10:90

while α-haloesters are very unreactive, only trichloroacetic[6] and halomalonic acid[7] derivatives giving alkoxyvinyl phosphates. Most substituents on the α-carbon atom e.g. alkyl groups and also strongly electron withdrawing groups e.g. halogen and carbonyl groups, promote the Perkow reaction and decrease the yield of alkylated product. It should be pointed out, however, that electron withdrawing substituents will also favour reaction at carbonyl oxygen and halogen atoms in addition to reaction at the carbonyl carbon atom.

(3) A change in halogen from chlorine to iodine decreases the yield of enol phosphate as shown by the data of Table 1, although the overall reactivity is in the usual order I > Br > Cl.[8]

It is also noted that an increase in temperature favours the Arbuzov reaction leading to phosphonates (S_N2 displacement), a conclusion which is supported by ample data on the variation of the product ratio with temperature in the absence of solvent.[1,8]

[6] M. S. Kharasch and I. S. Bengelsdorf, *J. Org. Chem.* **20**, 1356 (1955).

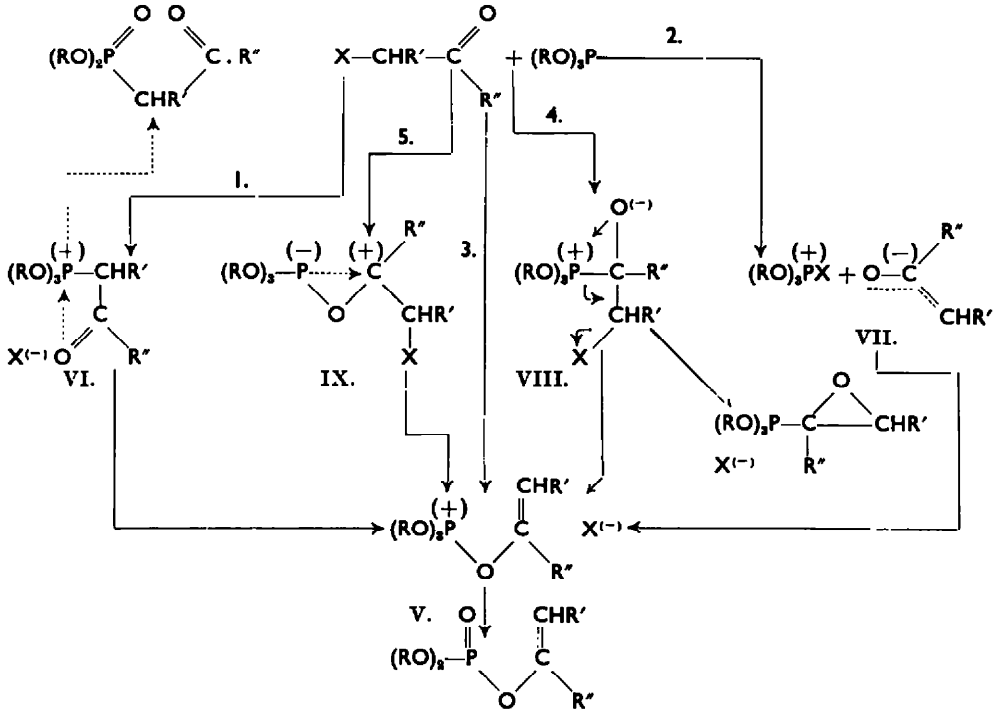
[7] F. Cramer and K. G. Gärtner, *Chem. Ber.* **91**, 704 (1959).

[8] A. N. Pudovik and V. P. Avery'anova, *Zh. Obsh. Khim.* **26**, 1426 (1956) *Chem. Abstr.* **50**, 14512 (1956).

Several mechanisms, summarized in the following chart, have been suggested for the Perkow reaction corresponding to initial attack by the nucleophilic phosphorus atom on the saturated carbon atom (I), the carbonyl carbon atom (2) the carbonyl oxygen atom (3) and more recently the halogen atom (4) in all cases leading to a quasi-phosphonium intermediate (V).

Since the dealkylation of V is irreversible and gives a stable product, it will be the last step of the reaction.

CHART 1. POSSIBLE MECHANISMS FOR THE PERKOW REACTION



In our following discussion we shall deal only with the preceding stages since these are the mechanistic steps which remain in doubt. The various alternatives given in the above scheme will now be considered in detail.

(1) *Attack at the α-carbon atom*

This proposal has received considerable support. Originally proposed by Perkow[9] and modified by Spencer *et al.*,[10] it has been developed further by Cramer.[11] The formation of the intermediate (VI) is reasonable since the displacement of halide ion by phosphite is known to occur under the conditions of the reaction,[12] and the subsequent rearrangement is similar to that observed in the Wittig reaction. The analogy is however not a good one since the negatively charged oxygen atom of the betaine intermediate of the Wittig reaction is highly nucleophilic compared with the carbonyl oxygen atom.

[9] W. Perkow, *Chem. Ber.* **87**, 755 (1954); W. Perkow, E. W. Krockow and K. Knoevenagel, *Ibid.* **88**, 662, (1955).

[10] E. Y. Spencer, A. R. Todd and R. F. Webb. *J. Chem. Soc.* 2968 (1958).

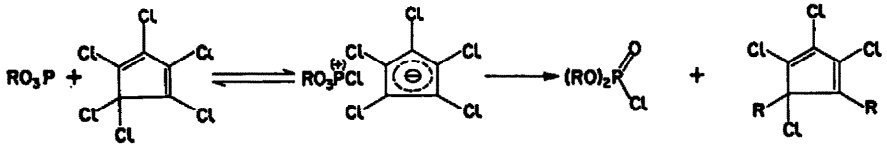
[11] F. Cramer, *Angew Chem.* **72**, 236 (1960).

[12] G. M. Koslapoff, *Organophosphorus compounds*, J. Wiley, New York (1958).

A number of stable ketophosphonium compounds have been prepared from triaryl[13] and trialkylphosphines,[14] and these show no tendency to rearrange. In order to settle the matter, we prepared two 2-ketophosphonium compounds $(CH_3O)_3\overset{(+)}{P}CH_2COR'$, ($R' = CH_3$ or COOEt) as their perchlorates in benzene solution. These compounds were identified by their IR spectra (which showed them to be stable to rearrangement) and by the rapid formation of the N-methylquinolinium cation on introducing quinoline into the solution. Phosphonate esters are dealkylated only slowly by this base. Thus initial attack on the α-carbon atom can be ruled out.

(2) *Attack on the halogen atom*

This mechanism has recently been suggested by analogy with the reactions of triphenylphosphine with chloral and phenacyl bromide,[5] and of dialkyl phosphites with 4-bromocyclohexadienones.[15] Nucleophilic attack by phosphites on positive halogen is well known e.g. the preparation of phosphorohalidates and the reactions with penta and hexachlorocyclopentadiene,[16] viz.



This is however not a likely mechanism for the Perkow reaction for the following reasons.

Whereas α-bromocyclohexanone reacts very rapidly at 0° with triphenylphosphine involving displacement on bromine while α-chlorocyclohexanone is completely inert[17a], phosphites show comparable reactivities with these haloketones. Moreover we find that good yields of enolphosphates can be obtained from both chloro and bromoketones in hydroxylic solvents. Thus phenacyl chloride and triethyl phosphite gave ca. 70% of vinyl ester on reaction in ethanol.[17b] Similarly bromopyruvic acid and its ethyl ester gave enol phosphate esters[18] on reaction with trimethyl phosphite in methanol. The product composition of the reaction between trimethyl phosphite and bromoacetone in methanol is not greatly different from that obtained in reactions in other solvents, although a hydroxylic solvent tends to produce a greater yield of the vinyl phosphate relative to the β-ketophosphate.

Since the mechanism involving initial attack on halogen leads to an ion pair (VII) which, by analogy with the corresponding ion pairs produced from triphenylphosphine and bromoketones and bromolactones would be very sensitive to hydroxylic

[13] A. Michaelis and E. Kohler, *Ber. Dtsch. Chem. Ges.* **32**, 1566 (1899); F. Ramirez and S. Dershowitz; *J. Org. Chem.* **22**, 41 (1957).

[14] W. Caldwell, *J. Chem. Soc.* **109**, 283 (1916); A. Michaelis, A. **315**, 43 (1901).

[15] B. Miller, *J. Org. Chem.* **26**, 4781 (1961); *Ibid.* **28**, 345 (1963).

[16] V. Mark, *Tetrahedron Letters* No 9, 295 (1961).

[17] [a] P. A. Chopard, R. F. Hudson and G. Klopman, *J. Chem. Soc.* 1379 (1965); [b] R. F. Hudson, P. A. Chopard and G. Salvadori, *Helv. Chim. Acta* **47**, 635 (1964).

[18] F. Cramer and D. Voges, *Chem. Ber.* **92**, 952 (1959); V. M. Clark and A. J. Kirby, *Biochim. Biophys. Acta* in press.

molecules,[5,19] such a mechanism can hardly lead to high yields of enol phosphates in alcoholic media.

TABLE 2. THE REACTION OF TRIMETHYLPHOSPHITE AND BROMOACETONE IN VARIOUS SOLVENTS

Solvent	Temp	Yield(%) vinyl phosphate	Yield(%) β-ketophosphonate
Ether	30°	30	35
Methanol	room temp	65	traces
	60°	55	28
T.H.F.	60°	30	55
None	110°	55	45

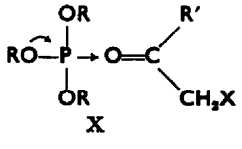
A further objection to this mechanism is the change in product composition with the nature of the halogen (Table 1). If the enol ester is produced by initial attack on halogen, it is difficult to see why the Arbuzov reaction should be favoured by increasing the electrophilic power of the halogen i.e. in the order I > Br > Cl. On the contrary, the reverse order would be expected, in view of the very large difference in electrophilic reactivity of the halogen atom in α-chloro and α-bromocyclohexanone.

For these various reasons therefore attack on halogen, which undoubtedly occurs in the reactions of bromoketones with triphenylphosphine,[5] is not a likely mechanism for the Perkow reaction, except perhaps in the reactions of compounds where the halogen is very positive.

(3) *Attack on carbonyl oxygen*

We are left therefore with mechanisms 3 and 4 as the most likely ones. Direct attack on oxygen, which has the advantage of being the simplest route has been suggested by several authors,[19,20] although no compelling evidence for this mechanism has been advanced. Our comparison between the reactivity of triphenylphosphine[17] and trimethyl phosphite towards α-chlorocyclohexane in fact argues against such a mechanism. Whereas the Perkow reaction proceeds normally at room temperature, the reaction with triphenylphosphine is extremely slow even at 100°–140° (estimated reactivity difference ca.10^6). This difference is difficult to understand if both reactions proceed on carbonyl oxygen since triphenylphosphine is considerably more reactive than trialkyl phosphites in S_N2 reactions, but is reasonable if the initial reactions are on the carbonyl or saturated carbon atoms (see later).

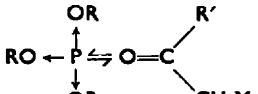
If initial attack occurs on carbonyl oxygen, an explanation of the high reactivity of trialkyl phosphites compared with tertiary phosphines must be given. There are several possibilities, for example electromeric release from the alkoxy group if bond formation is more advanced in this reaction than in the corresponding S_N2 process. Such an activation would explain why at least one alkoxy group is necessary for reaction (see p. 1962).



[19] S. Trippett, *J. Chem. Soc.* 2337 (1962); *Proc. Chem. Soc.* 106 (1962).

[20] G. Kamai and V. A. Kukhtin, *Dokl. Akad. Nauk SSSR* **112**, 868 (1957); A. N. Pudovik, *Zh. Obsh. Khim.* **25**, 2173 (1955); V. A. Kukhtin and A. N. Pudovik, *Uspekhi Khim.* **28**, 96 (1959).

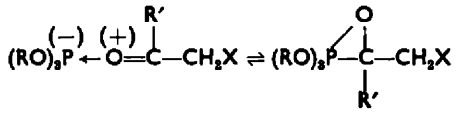
Alternatively, stabilization of the transition state by d_π bonding XI may be invoked, a process which is assisted by the electron attracting alkoxy groups.*



XI.

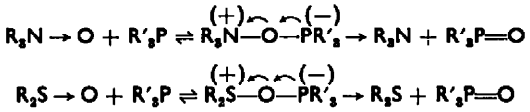
It is difficult to see however how this bonding assists the breaking of the CH_2-X bond, which must occur in the rate determining step in view of the reactivity order I > Br > Cl.

Another possibility is the nucleophilic attack by carbonyl oxygen on phosphorus followed by the rapid (or simultaneous) formation of a cyclic intermediate (XII).



XII.

An interaction of this kind is thought to occur in the reduction of amine oxides[21] and dialkyl sulphoxides[22] by tervalent phosphorus compounds,[21] viz.

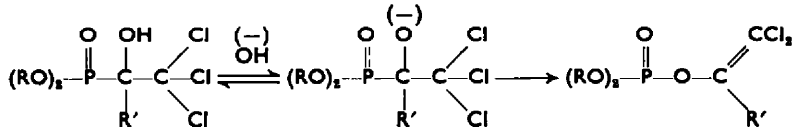


the rate order $(RO)_3P \gg R_3P$ having been observed in both cases. The nucleophilic power of the carbonyl oxygen atom should thus be decreased by the presence of electronegative substituents but the reverse effect is observed,[1] and this mechanism is therefore an improbable one for the Perkow reaction.

(4) *Attack on carbonyl carbon*

The carbonyl group is the most electrophilic centre at which dialkyl phosphites and their anions react to give α-hydroxyphosphonates and epoxy-phosphonates respectively.[2] By analogy, several workers[4b,6] have suggested that trialkyl phosphites react similarly to give the intermediate (VIII) which rearranges via the intermediate (XII) postulated in an alternative mechanism.

There are several analogies to the proposed rearrangement[23,24] viz.



* This was suggested to us independently by Drs. R. A. Shaw and B. Saville.

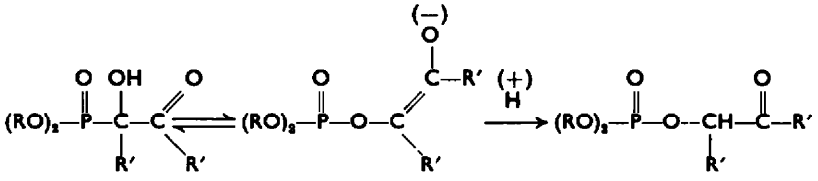
[21] See J. I. G. Cadogan, *Quart. Rev.* **16**, 214 (1962).

[22] R. A. Shaw, private communication.

[23] W. F. Barthel, B. H. Alexander, P. A. Giaug, S. A. Hall; *J. Amer. Chem. Soc.* **77**, 2424 (1955); R. Mühlmann and G. Schrader, *Z. Naturforsch.* **12b**, 196 (1957).

[24] V. A. Kukhtin, V. S. Abramov and K. M. Orekhova. *Dokl. Akad. Nauk SSSR* **128**, 1198 (1959); *Chem. Abstr.* **54**, 7536 (1960).

and

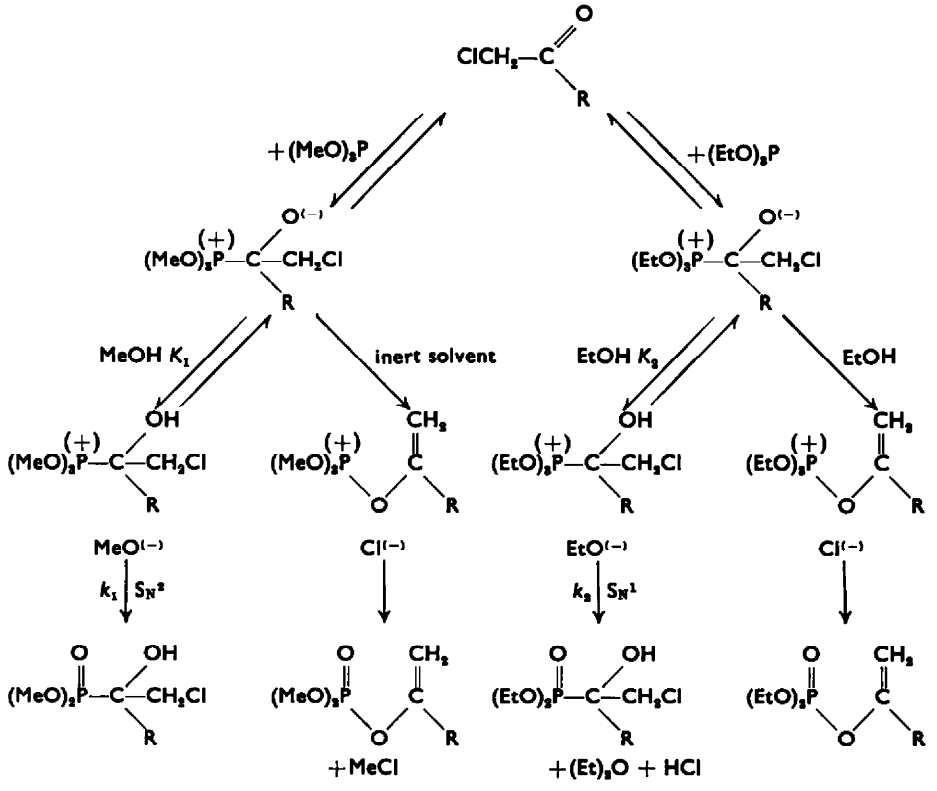


and the similar rearrangement of a quasi phosphonium intermediate (VIII) would be very much faster, and therefore could compete with de-alkylation. The absence of epoxides in the products of the Perkow reaction may be readily attributed to the greater electrophilic power of the $\overset{(+)}{P}$ centre compared with the saturated carbon atom.

Evidence for such an intermediate is found in the isolation of fair yields (~50%) of α-hydroxyphosphonates (type VIII,) from the reactions of chloroacetone and phenacyl chloride with trimethyl phosphite in methanol. (Under these conditions only 15–30% of enol ester is obtained.)

We have already noted however that in ethanol, these chloroketones give high yields of enol ester with ethyl phosphite.[17b] Moreover bromoketones, bromopyruvic acid and ethyl bromopyruvate also give enol phosphates in good yield in methanol solution.

The change in the course of the reaction with relatively small changes in the nature of the solvent is explained by the following scheme.



Since the pK of ethanol is about 2·6 units higher than that of methanol, and since the dealkylation of the ethoxy intermediate is slower than the corresponding methoxy-compound, it follows that $K_1 > K_2$ and $k_1 > k_2$. Consequently $K_1k_1 \gg K_2k_2$ and, in the case of the ethyl derivative, the vinyl ester is obtained almost exclusively.

The change in reaction products in the case of the bromo-compounds in methanol is explained by an increase in the value of k_1 owing to the greater lability of bromine than chlorine. If the reaction is carried out in a more acidic solvent e.g. acetic acid, K_1 is increased and the α-hydroxy-α-bromomethylphosphonate is obtained. (Table 3.)

TABLE 3. THE REACTION OF CH_3-CO-CH_2X and TRIALKYL-PHOSPHITES IN HYDROXYLIC SOLVENTS AT 25°

Solvent	Phosphite	Halogen X	Products
Ethanol (pK_a 19·1)	$(EtO)_3P$	Chloride*	66% A
Methanol (pK_a 16·7)	$(MeO)_3P$	Bromide	65% A
			55% A; 28% C (at 60°)
Methanol (pK_a 16·7)	$(MeO)_3P$	Chloride	15% A; 50% B
Acetic acid (pK_a 12·8)	$(MeO)_3P$	Bromide	30% A; 35% B

* phenacyl chloride; A = enol phosphate;
B = α-hydroxyphosphonate;
C: β-ketophosphonate.

This interpretation does not eliminate the alternative mechanism involving direct attack on carbonyl oxygen, since the formation of the adduct is reversible. Although it is highly likely that the Perkow reaction involves preliminary reaction at the carbonyl group—in contrast to the reaction of phosphine which normally proceeds at the saturated carbon atom (or halogen atom if this is bromine or iodine)—further work is necessary to determine the nature of the transition state of this reaction.

EXPERIMENTAL

Reactions of trialkyl phosphites with α-haloketones

a. *In the presence of silver ion.* A solution of trimethyl phosphite (2·8 g) and silver perchlorate (4·7 g) in dry benzene (100 ml) was added to iodoacetone (3·9 g) in benzene (120 ml) at 0°. No temp rise was evident, but precipitation of AgI began immediately. After 1 hr the solution spectrum at room temp showed no absorption between 1600–1700 cm^{-1} in the IR (i.e. no C—C absorption), no P=O band, but strong bands at 1710 cm^{-1} (C=O stretch) and 1040 cm^{-1} ($ClO_4^{(-)}$). This spectrum was unchanged after 4 days at room temp and after heating to reflux for a further 4 hr. Thus the β-ketophosphonium perchlorate $(MeO)_3P^{(+)}CH_2COCH_3 \cdot ClO_4^-$, present in solution, was stable under these conditions.

Addition of a small excess of quinoline to an aliquot of solution gave, almost immediately, a crystalline precipitate, identified as N-methylquinolinium perchlorate by comparison (IR spectrum) with an authentic sample prepared from the quaternary iodide and silver perchlorate in MeOH. Recrystallization from EtOH gave long, silky needles. (Found: C, 49·5; H, 4·4; N, 5·87. Calc. for $C_{10}H_{10}NClO_4$: C, 49·4; H, 4·2; N, 5·80%).

The IR spectrum of the filtered solution was that expected for the ketophosphonate $(MeO)_2P(O)$-CH_2COCH_3 (strong bands at ca. 1710, 1280, 1050 and 860 cm^{-1}).

Ketophosphonium perchlorates were also obtained in solution using (I) chloroacetone and (II) ethyl bromopyruvate in place of iodoacetone.

Reations of ethyl bromopyruvate and bromopyruvic acid in methanol

(a) Ethyl bromopyruvate[25] (2·2 g, 0·011 mole) was added to a solution of trimethyl phosphite (1·4 g, 0·011 mole) in MeOH (8 ml): an exothermic reaction took place. Removal of the solvent under red. press. left a liquid with the same IR spectrum (bands at 1740, 1640, 1290, 1180, 860, 830 cm^{-1}) as a sample of dimethyl-1-carbethoxyvinylphosphate prepared from the same reagents in ether. This product had b.p. 106–109°/0·5 mm. (Found: C, 37·1; H, 5·8. Calc. for $C_7H_{13}PO_6$: C, 37·4; H, 5·8%).

(b) Bromopyruvic acid[26] (6·7 g, 0·04 mole) was added to a solution of trimethyl phosphite (5·0 g, 0·04 mole) in MeOH (40 ml): an exothermic reaction took place. Removal of the solvent under red. press. gave a liquid with an IR spectrum (strong bands at 1735, 1635, 1260, 1170, 1040 and 860 cm^{-1}) identical with that of a sample of dimethyl 1-carboxyvinylphosphate prepared by the same reaction in ether.

Reaction of trimethyl phosphite with chloroacetone in methanol

Trimethyl phosphite (24·8 g; 0·2 mole) was added rapidly with stirring to a solution of chloroacetone (18·4 g; 0·2 mole) in dry MeOH (150 ml). A slightly exothermic reaction resulted. The mixture was left overnight and the solvent removed. Distillation of the residue gave *dimethyl-1-methylvinylphosphate*, 7 g (15%), b.p. 35–40°, 0·005 mm identified comparison with an authentic sample and *dimethyl-α-hydroxy-α-chloromethyl-ethylphosphonate*, 21 g (46%) b.p. 105–107° 0·005 mm, m.p. 81–82° (cyclohexane). (Found: C, 29·8; H, 6·25; Cl, 17·6; P, 15·3. Calc. for $C_5H_{12}ClO_4P$: C, 29·6; H, 5·96; Cl, 17·5; P, 15·3%).

The NMR spectrum was consistent with this structure, since the $C\text{-}CH_3$, $O\text{-}CH_3$ and O-H were all doublets (τ = 8·49, 6·12 and 4·43 respectively; J_{PH} = 15·5, 10·0 and 4·0 c/s. respectively). Dimethyl phosphite gave no reaction under these conditions.

Reaction of trimethyl phosphite with phenacyl chloride in methanol

Trimethyl phosphite (24·8 g, 0·2 mole) was added rapidly with stirring to a solution of phenacyl chloride (30·9 g; 0·2 mole) in MeOH (150 moles). The temp rose to 35–40° and the mixture became yellow. After leaving the mixture overnight, the solvent was partly removed, which allowed the crystallization of *dimethyl-α-hydroxy-α-chloromethyl-benzylphosphonate*, 15 g, 30%, m.p. 144–146° (MeOH). (Found: C, 46·0; H, 5·13; Cl, 13·4; P, 12·1. Calc. for $C_{10}H_{13}ClO_4P$: C, 45·7; H, 5·33; Cl, 13·4; P, 11·7%).

Distillation of the residue gave in addition to some unreacted phenacyl chloride, *dimethyl-1-phenylvinyl phosphate*, 15·4 g (30%) b.p. 112–114°, 0·01 mm, identified by comparison with the corresponding ethyl ester.

Reaction of trimethyl phosphite with α-bromoacetone

This reaction was carried out in the following solvents with the same molar concentrations as previously.

a. *In refluxing methanol.* Distillation gave 55% vinyl ester and 28% dimethyl acetonyl phosphonate, b.p. 53–54°, 0·03 mm, n_D^{22} = 1·4335 (lit.[8] n_D^{20} = 1·4337) identified by comparison with an authentic specimen.

b. *In methanol at room temperature.* The above reaction at room temp was rather more vigorous than the corresponding one with chloroacetone. On distillation, 65% of the vinyl ester and only traces of the β-ketophosphonate were collected. No α-hydroxy ester was observed.

c. The corresponding reaction in *ether at* 30°, *THF* at 60° and *neat at* 110–120° gave respectively the following ratios for the % yields of vinyl ester to β-ketoester: 30/35; 30/55; 55/45.

d. *In acetic acid at room temperature.* Distillation gave 30% of the vinyl ester, and *dimethyl-α-hydroxy-α-bromomethylethylphosphonate* (27%), b.p. 123–127°, 0·15 mm, the IR spectrum of which was very similar to the one of the corresponding chloro derivative. (Found: C, 24·7; H, 5·1. Calc. for $C_5H_{12}BrO_4P$: C, 24·3; H, 4·9%). At higher concentrations in acetic acid, the formation of the vinyl ester was favoured at the expense of the α-hydroxyphosphonate.

[25] P. F. Krux, N. Geurkink and K. L. Grist, *J. Amer. Chem. Soc.* **76**, 5796 (1954).
[26] Sprinson and Chargaff, *J. Biol. Chem.* **164**, 417 (1946).