Reaction Of Alpha-haloketones With Tertiary Phosphines.

Citation

VIRKHAUS, REIN. *Reaction Of Alpha-Haloketones With Tertiary Phosphines.* 1965, https://preserve.lehigh.edu/lehigh-scholarship/graduate-publications-theses-dissertations/theses-dissertations/reaction-alpha.

VIRKHAUS, Rein, 1938–
REACTION OF α–HALOKETONES WITH
TERTIARY PHOSPHINES.

Lehigh University, Ph.D., 1965
Chemistry, organic

University Microfilms, Inc., Ann Arbor, Michigan

REACTION OF α-HALOKETONES WITH TERTIARY PHOSPHINES

by
Rein Virkhaus

A DISSERTATION

Presented to the Graduate Faculty

of Lehigh University

in Candidacy for the degree of

Doctor of Philosophy

Lehigh University

1965

This dissertation is respectfully submitted to the Graduate Faculty of Lehigh University, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

Rein Virkhaus

Rein Virkhaus

A CERTIFICATE OF APPROVAL

Approved and recommended for acceptance as a dissertation in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

Accepted: MAY 25, 1965   I J Borowitz
Date   Professor in Charge

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ACKNOWLEDGEMENTS

The author wishes to extend his sincere thanks to Dr. I. J. Borowitz both for the suggestion of the problem and for the advice and encouragement during the course of the research. He also gratefully acknowledges his indebtedness to his Special Committee and to Dr. V. B. Fish for their valuable assistance; to Dr. C. E. Griffin for some NMR spectra; and to Miss Roberta Wagner for typing this manuscript.

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ABSTRACT

The reactions of several alpha-bromo- and alpha-chloroketones with triphenylphosphine were studied. The reaction of phenacyl bromide with triphenylphosphine gave phenacyltriphenylphosphonium bromide in 80-85% yield in benzene or acetonitrile. The yield of the phosphonium salt was decreased to 9% and an 88% yield of acetophenone was obtained in the presence of excess methanol. It is postulated that initial reaction involves attack on bromine by the phosphine to give an enolate bromophosphonium ion-pair which then interacts to give the C-phosphonium salt in non-protic solvents. In the presence of methanol the ion-pair is converted to the dehalogenated ketone, triphenylphosphine oxide and methyl bromide. The initial presence of dimedone gave a smaller amount of interception.

Alpha-bromopropiophenone reacted with triphenylphosphine more slowly but in a similar manner. Alpha-bromoisobutyrophenone reacted with triphenylphosphine to yield primarily isobutyrophenone (in benzene or methanol) and smaller amounts of methacrylophenone. None of the alpha-C-phosphonium salt

was formed. A 48% yield of the beta-C-phosphonium salt was formed in acetonitrile.

The reaction of desyl bromide with triphenylphosphine in various solvents led to a mixture of the C-phosphonium salt (58% in benzene), the corresponding ylid, deoxybenzoin and diphenylacetylene. The sole product in methanol was deoxybenzoin (100% yield). Desyl chloride reacted more slowly but also gave mixtures of the above-mentioned products.

In contrast to the above results, phenacyl chloride or alpha- chloroacetone reacted with triphenylphosphine either in benzene or methanol to give the corresponding C-phosphonium chlorides. These reactions appear to proceed by S_N2 displacement of chloride ion.

The reactions of alpha, alpha-dibromo- and alpha, alpha-dichlorodeoxybenzoin gave, among other products, diphenylacetylene in 49 and 31% yields respectively.

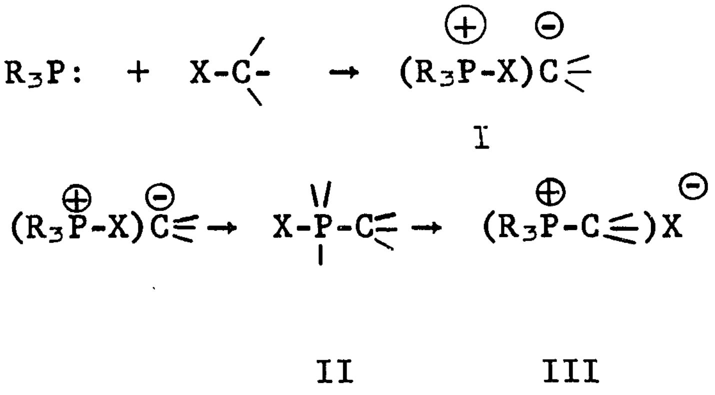
The possible mechanistic pathways for these reactions are discussed.

Introduction

The most evident property of trivalent organophosphorus compounds is their ability to utilize the unshared electron pair on phosphorus to form bonds to other atoms. In this respect, the phosphines resemble amines and are weakly basic compounds forming phosphonium salts with proton acids and adducts with Lewis acids. Tertiary phosphines, in particular, also act as strongly nucleophilic reagents, reacting with alkyl halides by attack at carbon to form phosphonium salts. The rate of reaction has long been observed to be dependent on the nature of both the phosphine and the alkyl halide used. However, despite the large number of compounds available, very few kinetic studies have been carried out and hence the relative rates of reaction are largely unknown. Henderson and Buckler(1), in a recent conductometric study, reported (1) that in a series of closely related tertiary phosphines the relative rate of reaction with ethyl iodide increases in the order: $(C_6H_5)_3P < (C_6H_5)_2PC_2H_5 < (p\text{-}CH_3O\text{-}C_6H_4)_3P < C_6H_5P(C_2H_5)_2 < (C_2H_5)_3P$; (2)

that in the reaction of tributylphosphine with a series of alkyl iodides (RI) the relative rates observed are: (R=) Me 5250, Et 31.2, n-Pr 12.9, n-Bu 11.5, i-Bu 1.0 and (3) that in the reaction of tributylphosphine with n-propylhalides the relative rate of reaction decreases sharply in the order: n-$C_3H_7I > $ n-$C_3H_7Br > $ n-C_3H_7Cl. Findings such as these have helped to create belief in the assumption that the effect of substituents on the formation of phosphonium salts by alkylation at carbon is, in general, the same as that for other more thoroughly studied S_N2 reactions.

However, because of the great tendency of phosphorus to form pentacovalent species and the ready polarizability of the halogen, the possibility arises that when attack at carbon of a carbon-halogen bond is sterically hindered or when strong electron acceptors polarize the carbon-halogen bond giving the halogen atom a partial positive charge and at the same time increasing the stability of the carbanion remaining, the site of nucleophilic attack may shift to the halogen atom. The removal of halogen as a cation gives initially ion-pair I which, through the intermediacy of the pentacovalent structure II, can yield the phosphonium salt III.



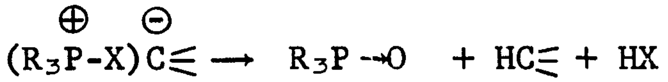
$$R_3P: + X\text{-}\overset{/}{\underset{\backslash}{C}}\text{-} \rightarrow (R_3\overset{\oplus}{P}\text{-}X)\overset{\ominus}{C}\leqslant$$

I

$$(R_3\overset{\oplus}{P}\text{-}X)\overset{\ominus}{C}\leqslant \rightarrow X\text{-}\overset{\backslash /}{\underset{|}{P}}\text{-}C\leqslant \rightarrow (R_3\overset{\oplus}{P}\text{-}C\leqslant)\overset{\ominus}{X}$$

II III

This reaction scheme can be distinguished from the direct S_N2 displacement of halide ion by the ready solvolysis of ion-pair I according to (eq. a).



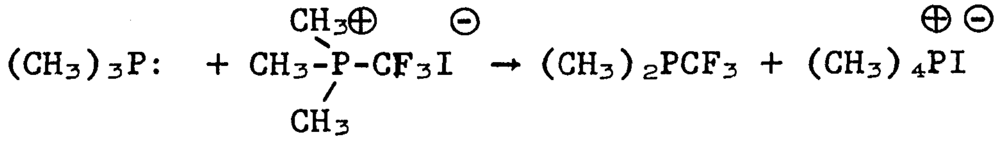
$$(R_3\overset{\oplus}{P}\text{-}X)\overset{\ominus}{C}\leqslant \longrightarrow R_3P\rightarrow O + HC\leqslant + HX \qquad (a)$$

Hence, if the yield of the phosphonium salt III is substantially lowered in solvolytic solvents in favor of the products of equation (a), the reaction under study involves initial attack on halogen.

A few examples illustrating these reactions will now be discussed.

Hazeldine and West[(2)] proposed that the reaction of trimethylphosphine with iodofluoromethane proceeds by an initial nucleophilic attack of the phosphine on the halogen (eq.b). The initially formed phosphonium iodide (IV) is demethylated by excess trimethylphosphine (eq.c).

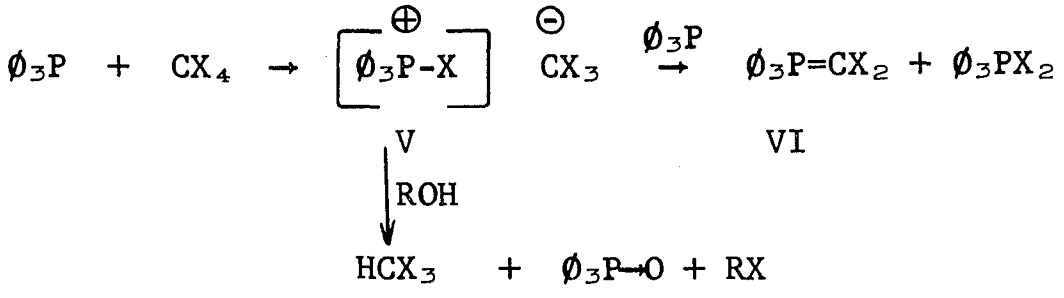
$$(CH_3)_3P: + ICF_3 \rightarrow ((CH_3)_3\overset{\oplus}{P}-I)\overset{\ominus}{CF_3} \rightarrow \underset{IV}{(CH_3)_3\overset{\oplus}{P}-CF_3\overset{\ominus}{I}} \qquad (b)$$



$$(CH_3)_3P: \quad + CH_3-\overset{CH_3\oplus}{\underset{CH_3}{P}}-CF_3\overset{\ominus}{I} \rightarrow (CH_3)_2PCF_3 + (CH_3)_4\overset{\oplus}{P}\overset{\ominus}{I} \qquad (c)$$

Trifluoroiodomethane reacts with hydroxide ions to yield trifluoromethane and hypoiodite(3) and with tertiary amines forms trifluoromethane.(2)

Carbon tetrachloride(4,5) and carbon tetrabromide(6) react with triphenylphosphine in inert solvents to give dihalomethylenephosphoranes VI and triphenylphosphine dihalides. In alcohol, the ion-pair V initially formed is solvolysed with formation of trihalomethane, phosphine oxide and alkyl halide.(5)



$$\emptyset_3P + CX_4 \rightarrow \underset{V}{\left[\overset{\oplus}{\emptyset_3P-X}\right]}\overset{\ominus}{CX_3} \xrightarrow{\emptyset_3P} \underset{VI}{\emptyset_3P=CX_2} + \emptyset_3PX_2$$

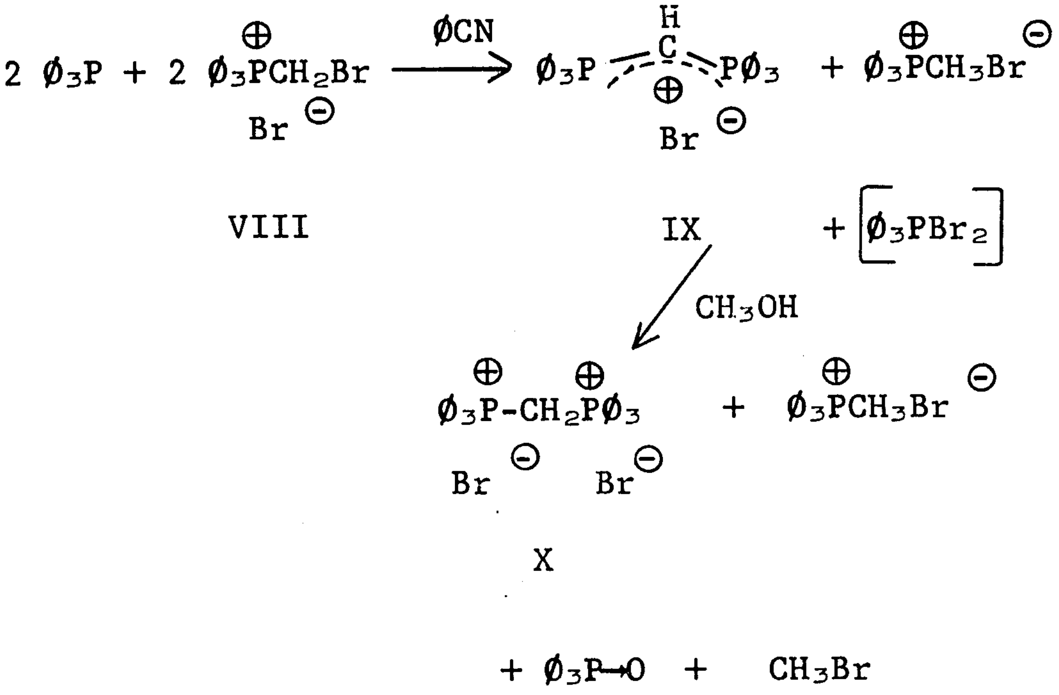
$$V \xrightarrow{ROH} HCX_3 + \emptyset_3P\rightarrow O + RX$$

Rabinowitz(4) found that the reaction of triphenylphosphine with carbon tetrachloride goes in total darkness and is not accelerated by free-radical initiators or by UV light. Furthermore, no dichlorotetramethylcyclopropane is formed in the presence of tetramethylethylene, although the latter is a better carbene scavenger than triphenylphosphine.(4) These results eliminate both free-radical and carbene mechanisms. ∝-Dibromomethyltriphenylphosphonium bromide (VII) is very readily debrominated by triphenylphosphine in wet methyllene chloride.(6) The first step again appears to be abstraction of "positive" bromine by the phosphorus.

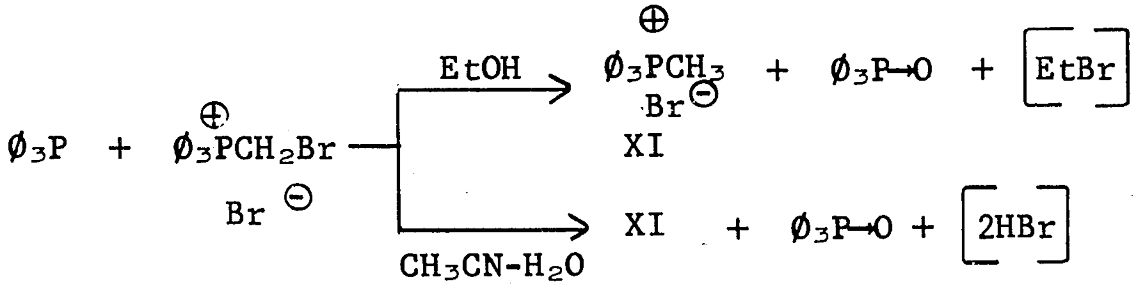
$$\phi_3\overset{\oplus}{\text{P}}\text{-CHBr}_2\overset{\ominus}{\text{Br}} + \phi_3\text{P} \xrightarrow{\text{5 min.}} \overset{\oplus\text{Br}\,\ominus}{\phi_3\text{P-CH}_2\text{Br}} + \phi_3\text{P} \rightarrow 0$$

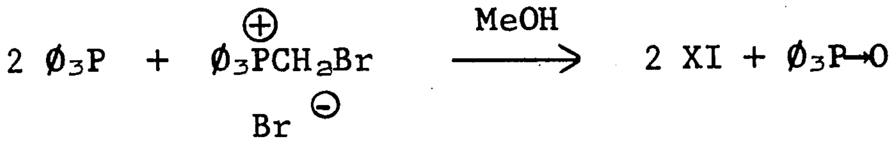
VII

The reaction course of triphenylphosphine with VIII has been studied in detail.(7) In an aprotic solvent such as benzonitrile, a bisphosphonium salt (IX) is formed. Yet, in the presence of oxygenated protic compounds neither of the methylenebis(phosphonium) salts IX or X is formed as reductive



dehalogenation takes place to give XI.

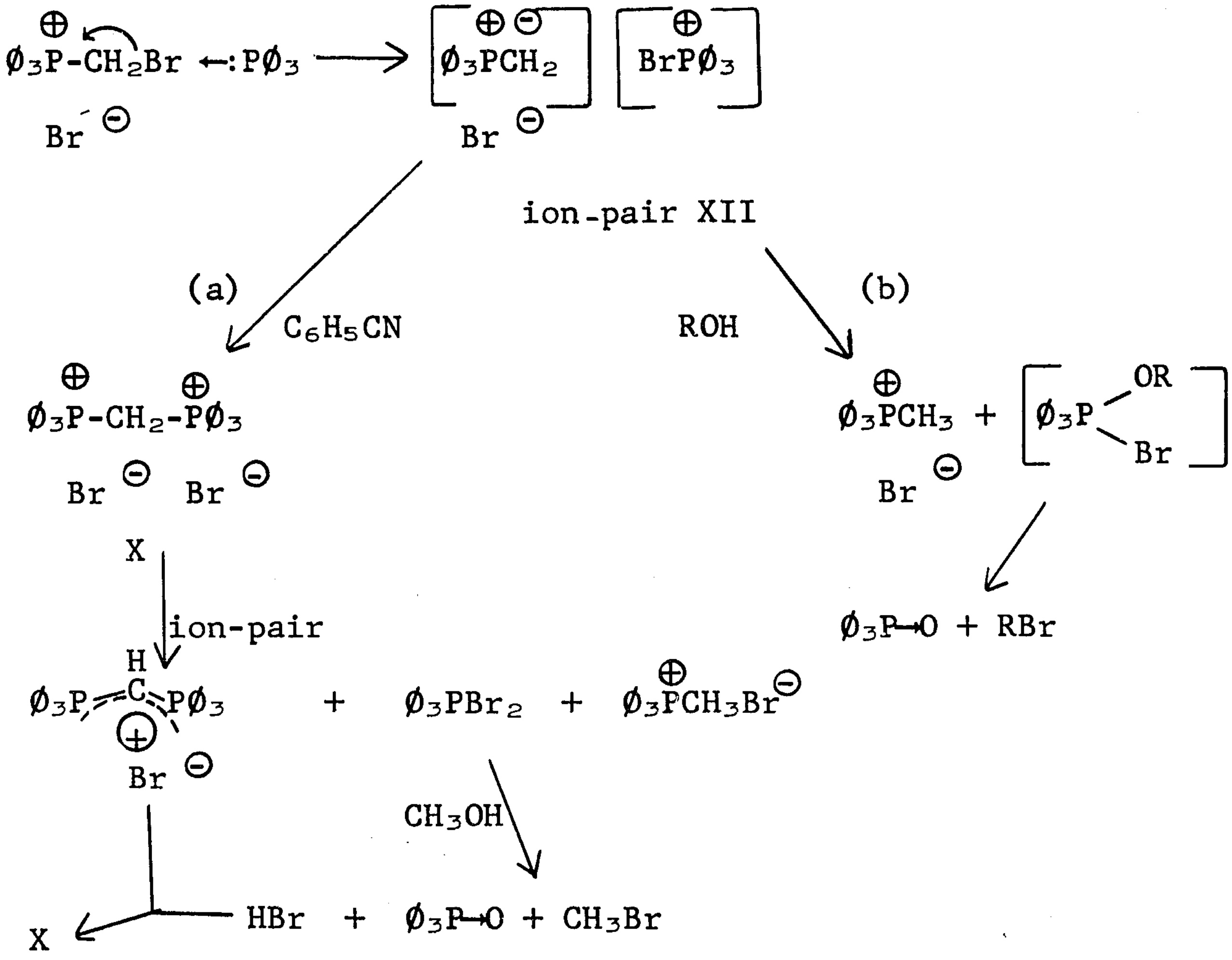




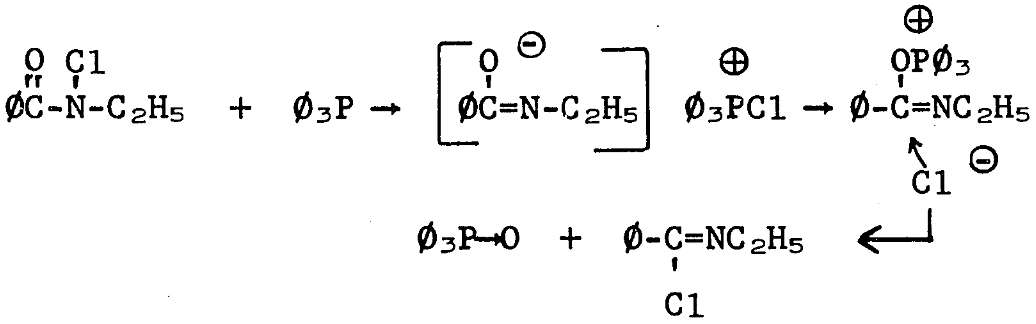
$$2\ \text{Ø}_3\text{P} + \overset{\oplus}{\text{Ø}_3\text{PCH}_2\text{Br}}\ \underset{\text{Br}^{\ominus}}{} \xrightarrow{\text{MeOH}} 2\ \text{XI} + \text{Ø}_3\text{P}{\rightarrow}\text{O}$$

The existence of methylenetriphenylphosphorane as a long-lived intermediate in this reaction was ruled out by the fact that added benzophenone failed to undergo a Wittig reaction.

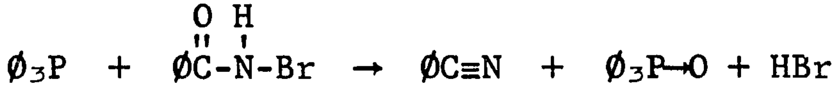
The reaction scheme proposed(7) is a nucleophilic attack of phosphorus on the bromine to form the ion-pair (XII). In aprotic solvents, reaction path (a) is followed and in protic solvents, where a rapid proton-transfer occurs between ROH and the ion-pair, path (b) predominates.



Triphenylphosphine reacts with N-chloro-N-ethyl benzamide to give an imidoyl chloride (eq.d). Speziale and Smith(8) suggested attack at chlorine as the first step. However, the possibility of initial attack on oxygen was not eliminated.

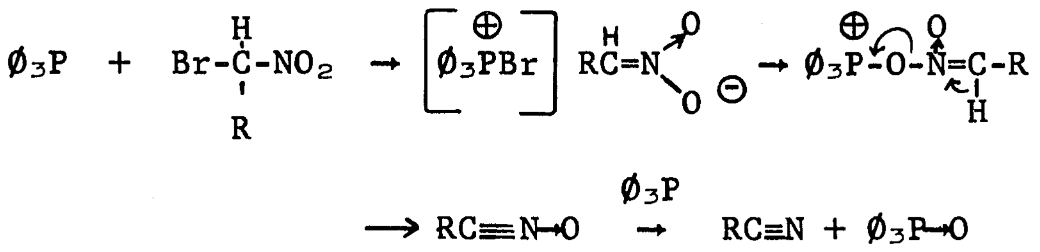

(d)

Similarly, reaction of triphenylphosphine with N-bromoamides gives triphenylphosphine oxide and nitriles (eq.e).(9)

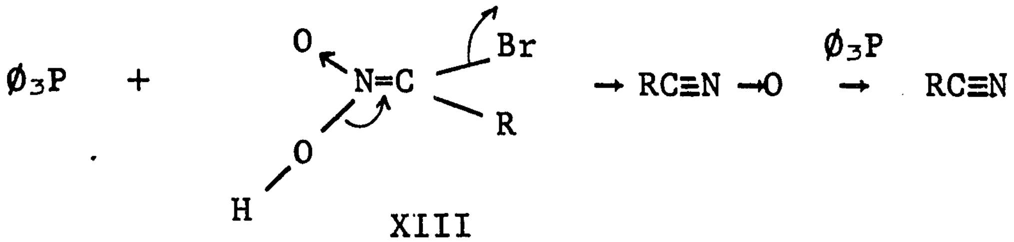

(e)

$$\phi_3P + \phi\overset{O}{\overset{\|}{C}}-\overset{H}{\overset{|}{N}}-Br \rightarrow \phi C{\equiv}N + \phi_3P{\rightarrow}O + HBr \qquad (e)$$

The initial attack could be again at halogen,(8) with reaction through the enolic form of the amide, attack on oxygen, as the alternate possibility.(9) Ion-pair intermediates have been proposed(8) to explain the formation of nitriles from the reaction of triphenylphosphine with α-bromonitro-propane, -octane or-phenylmethane:(9)

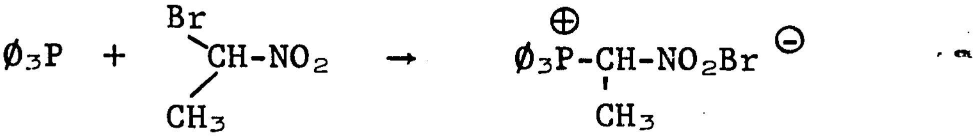


The original assumption(9) of attack by phosphorus on the oxygens of the aci forms (XIII) of the α-bromonitroalkanes seems, in view of more recent work,(8) less plausible:



XIII

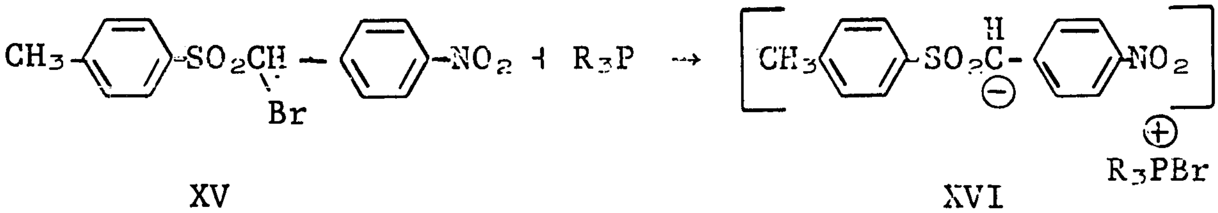
By contrast, however, α-bromonitroethane ($R=CH_3$) forms the phosphonium salt (XIV):



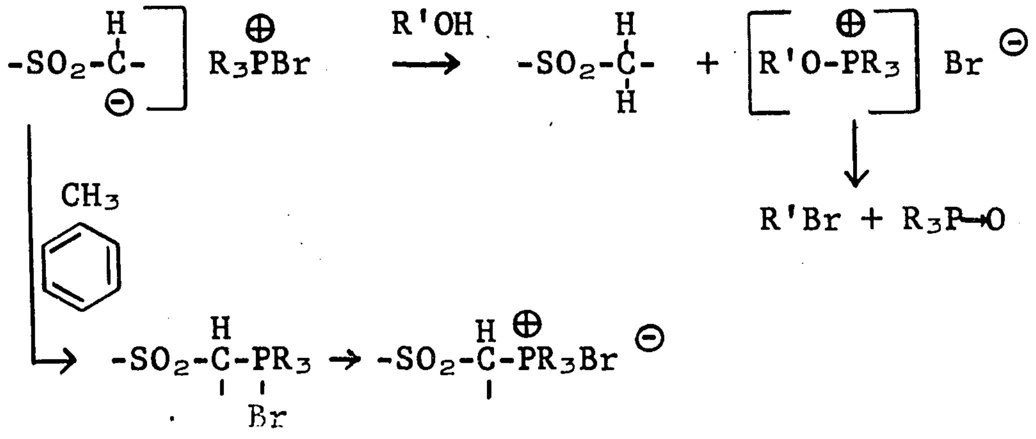
$$\phi_3P + \underset{CH_3}{\overset{Br}{CH}}-NO_2 \rightarrow \phi_3\overset{\oplus}{P}-\underset{CH_3}{CH}-NO_2Br^{\ominus}$$

XIV

Hoffmann and Forster(10) reported that the α-bromosulfone (XV) readily forms a phosphonium salt in toluene but that only dehalogenated sulfone, phosphine and hydrogen bromide (or alkyl bromide) are found if the reaction is performed in the presence of water or alcohol. The phosphonium salt is stable to hydrolysis and is not cleaved by boiling in methanol or acetic acid. These results were explained by the assumption that the initial step in the reaction is abstraction of the bromine cation to give an ion-pair XVI which is solvolysed in hydroxylic solvents (eq.f), but which gives a phosphonium salt in inert solvents by way of an unstable pentacovalent intermediate (XVII) (eq.g.).



XV XVI

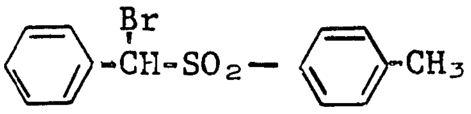


(f)

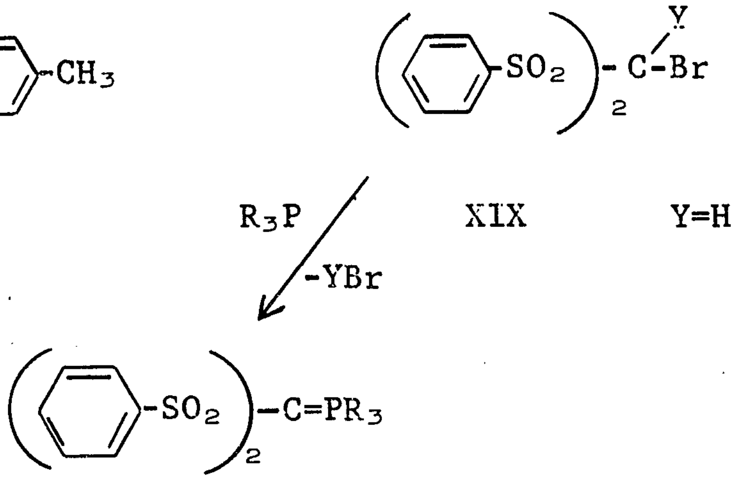
(g)

XVII

Similar results were obtained with the α-bromosulfone XVIII and with the bisphenylsulfonylbromomethanes XIX where the ylid XX is the final product. The rate of reaction was found to be XIX > XV >> XVIII.



XVIII

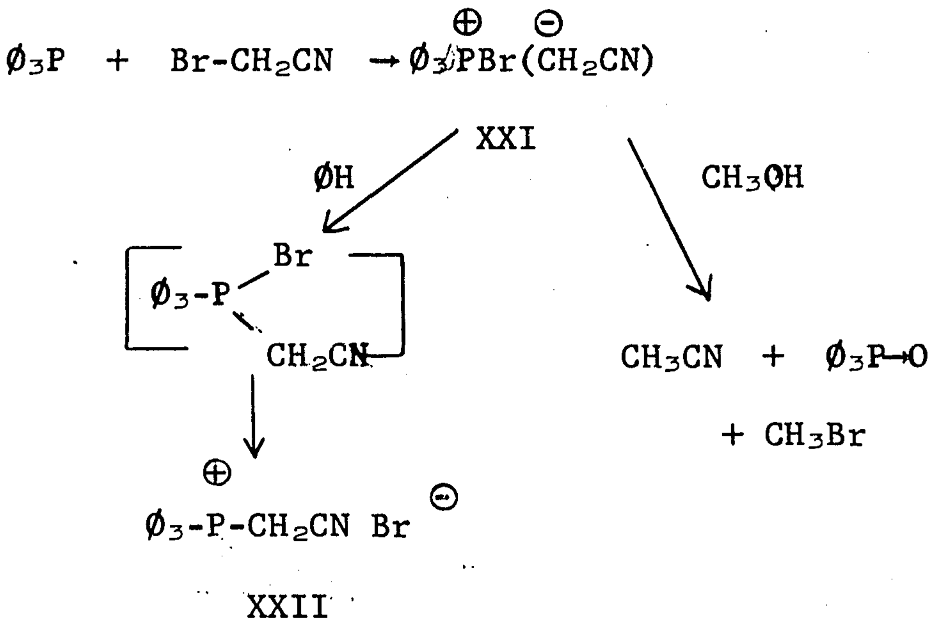


XIX

Y=H, Br

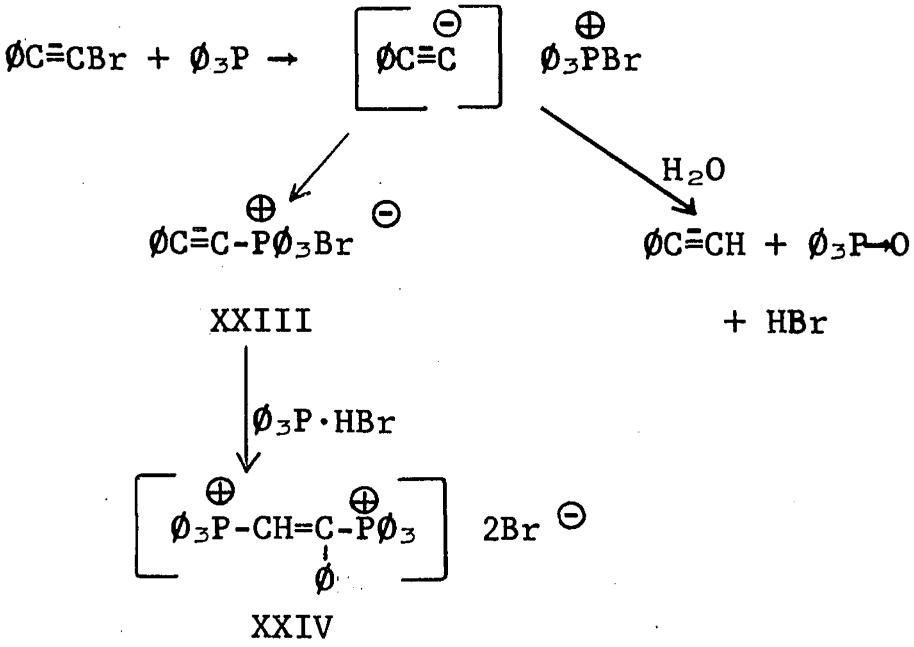
XX

Bromoacetonitrile and triphenylphosphine react in benzene to give cyanomethyltriphenylphosphonium bromide (XXII).(11) However, dehalogenation predominates in benzene-methanol. Since XXII is stable towards alcoholysis and since it was shown(11) that the reaction does not proceed by a free-radical mechanism, it again appears that a carbanion-bromophosphonium ion-pair (XXI) is initially formed:(8)



However, since formation of XXII is not entirely eliminated in presence of methanol, the rate of solvolysis of ion-pair XXI must be comparable with the rate of association to form XXII.

The formation of phenylethynyltriphenylphosphonium bromide (XXIII)$^{(12,13,14)}$ clearly proceeds by initial attack by the phosphine on the bromine atom rather than on the acetylenic carbon. Thus it has been found$^{(14)}$ that phenylbromoacetylene reacts with triphenylphosphine twenty times as rapidly as does n-butyl bromide. This result would hardly be expected if the reaction involved a simple S_N2 attack by the phosphine at the acetylenic carbon. Moreover, Hoffmann and Forster$^{(12)}$ have reported that when the reaction is performed in aqueous acetonitrile, half of the acetylenic compound isconverted to the bisphosphonium salt (XXIV), derived from XXIII, and the other half is dehalogenated to phenylacetylene. The following reaction scheme is postulated:



$$\phi C{\equiv}CBr + \phi_3P \rightarrow \left[\phi C{\equiv}\overset{\ominus}{C}\right] \quad \phi_3\overset{\oplus}{P}Br$$

$$\left[\phi C{\equiv}\overset{\ominus}{C}\right] \rightarrow \phi C{\equiv}C\text{-}\overset{\oplus}{P}\phi_3 Br^{\ominus}$$

XXIII

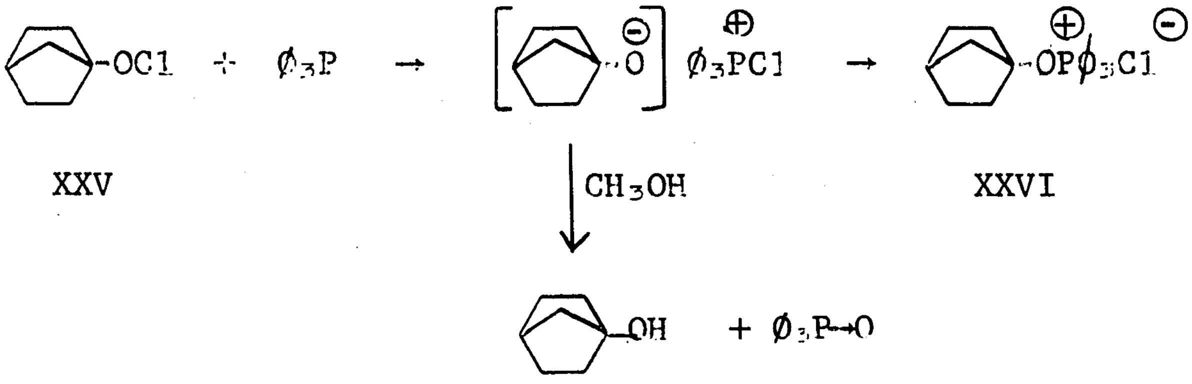
$$\left[\phi C{\equiv}\overset{\ominus}{C}\right] \xrightarrow{H_2O} \phi C{\equiv}CH + \phi_3P{\rightarrow}O + HBr$$

$$\text{XXIII} \xrightarrow{\phi_3P\cdot HBr} \left[\phi_3\overset{\oplus}{P}\text{-}CH{=}\underset{\phi}{C}\text{-}\overset{\oplus}{P}\phi_3\right] \quad 2Br^{\ominus}$$

XXIV

The fact that the formation of XXIII is only partly suppressed may be interpreted either as an indication of the equality of the rates of solvolysis and C-phosphonium salt formation or as a sign that XXIII can be formed by an alternate pathway in aqueous media.

Denney and DiLeone(15) found that triphenylphosphine reacts with the bridgehead hypochlorite (XXV) to give a phosphonium salt XXVI which is stable in methanol or water. Yet, when the methanol is initially present, the products obtained are bicyclo-[2,2,1]-heptanol-1 (XXVII) and triphenylphosphine oxide. Since S_N2 attack at the bridgehead is impossible, the initial attack must have occurred at the halogen atom to give the alkoxide chlorotriphenylphosphonium ion-pair, which is rapidly solvolysed by methanol.

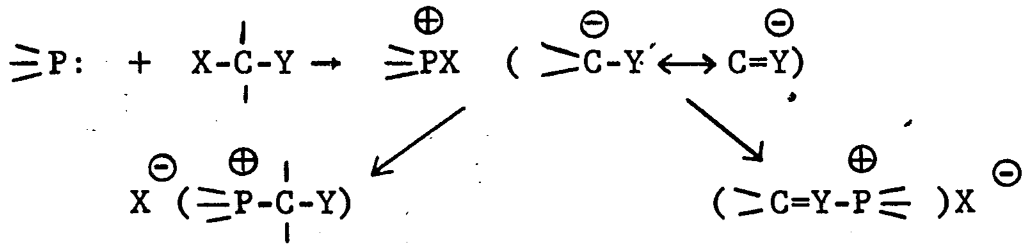


XXV

XXVI

XXVII

In the reaction of tertiary phosphines with those active halogen compounds where the carbanion of the intermediate ion-pair can be stabilized by resonance, the further possibility arises that in addition to or instead of the formation of the expected C-phosphonium salts XXVIII, other types of "onium" salts XXIX can be obtained in which the linkage to the phosphorus is through heteroatoms (eq.h).



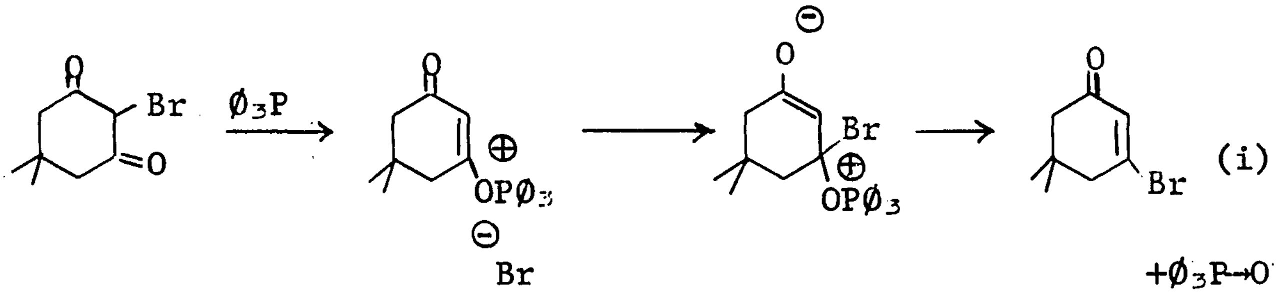
(h)

XXVIII XXIX

Unfortunately, compounds such as XXIX have proved to be extremely sensitive to moisture and, therefore, except for one instance, compound XLII, they have not been actually isolated. However, their existence has been shown indirectly in several cases.

The enol phosphonium salt (XXXI) has been proposed(16) as an intermediate in the reaction of 2-bromodimedone (XXX) with triphenylphosphine. Michael addition of bromide ion to

XXXI and subsequent elimination of triphenylphosphine oxide leads to XXXII. (eq.i).

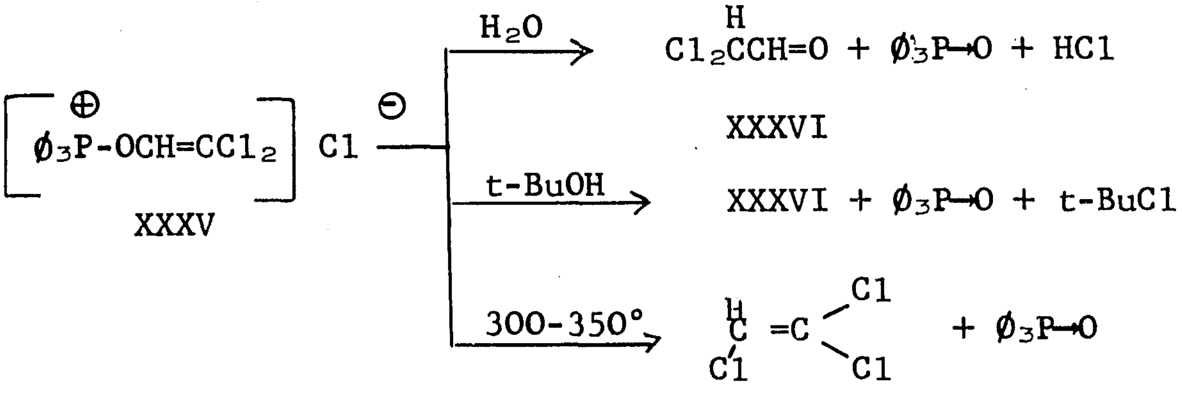


XXX XXXI XXXII

The reaction of triphenylphosphine with chloral (XXIV) in diethyl ether gives an adduct which is postulated to be the enol phosphonium salt (XXXV).(17,21)

$$\underset{\text{XXXIV}}{Cl_3CH{=}O} + \phi_3P \rightarrow \underset{\text{XXXV}}{\left[\overset{\oplus}{\phi_3P}\text{-}OCH{=}CCl_2\right]} \; Cl^{\ominus}$$

In the presence of water or alcohol XXXV decomposes to dichloroacetaldehyde (XXXVI) and triphenylphosphine oxide; upon heating, XXXV yields trichloroethylene (XXXVII).(17)

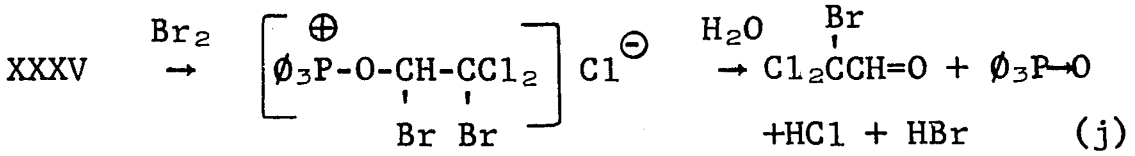


XXXV

XXXVI

XXXVII

The presence of a double bond in XXXV was shown by bromination and subsequent hydrolysis to the products shown in (eq.j.).

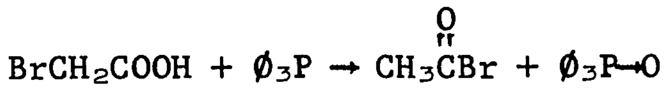


$$\mathrm{XXXV} \xrightarrow{Br_2} \left[\overset{\oplus}{\phi_3P}\text{-}O\text{-}\underset{Br}{CH}\text{-}\underset{Br}{CCl_2}\right] Cl^{\ominus} \xrightarrow{H_2O} Cl_2\overset{Br}{C}CH{=}O + \phi_3P{\rightarrow}O + HCl + HBr \qquad (j)$$

Chloroacetic acid reacts with triphenylphosphine to form a phosphonium salt$^{(18)}$ (XXXIX), but bromoacetic acid (XL) in benzene gives acetyl bromide and triphenylphosphine oxide.$^{(19,20)}$

$$ClCH_2COOH + \phi_3P \longrightarrow \phi_3\overset{\oplus}{P}\text{-}CH_2COOH\ Cl^{\ominus}$$

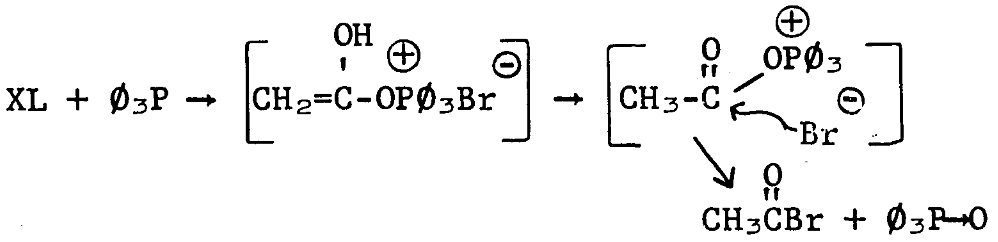
XXXIX



$$BrCH_2COOH + \phi_3P \rightarrow CH_3\overset{\overset{O}{\|}}{C}Br + \phi_3P\rightarrow O$$

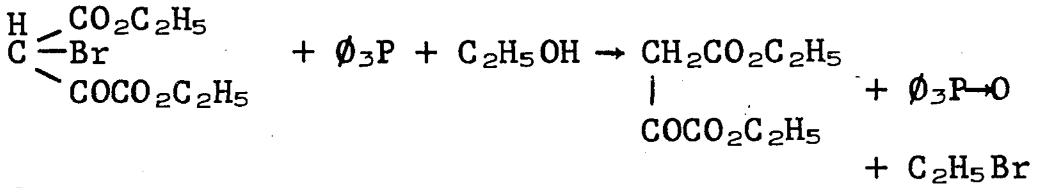
XL

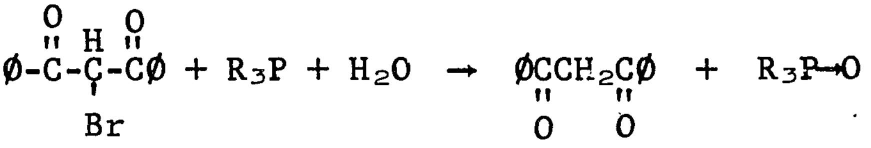
With XL, the reaction sequence shown in (eq.k) has been proposed.(19)



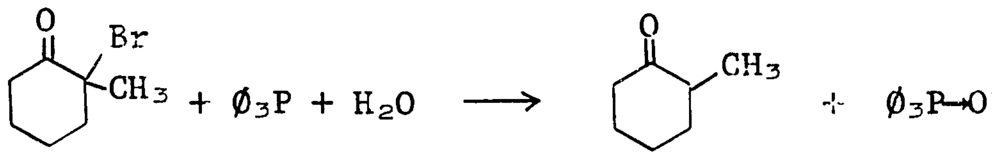
(k)

The dehalogenation of various secondary and tertiary α-halo carbonyl compounds is believed to proceed through the intermediacy of enol phosphonium salts.(16,17,21)



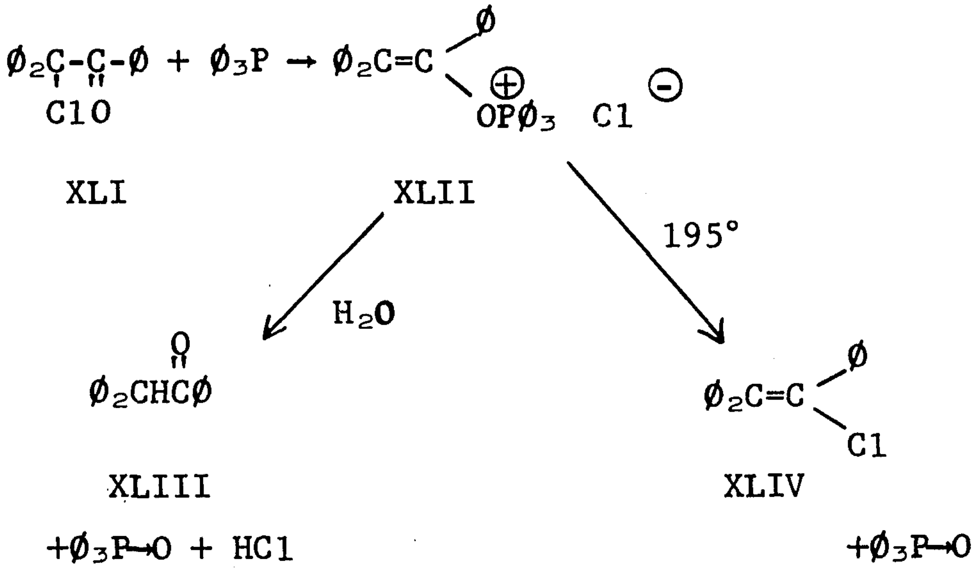


$$\phi\text{-}\overset{\overset{O}{\|}}{C}\text{-}\underset{Br}{\overset{H}{C}}\text{-}\overset{\overset{O}{\|}}{C}\phi + R_3P + H_2O \rightarrow \phi\underset{\overset{\|}{O}}{C}CH_2\underset{\overset{\|}{O}}{C}\phi + R_3P\rightarrow O$$



In each case, an initial adduct formed in an inert solvent is decomposed upon addition of a protic compound.

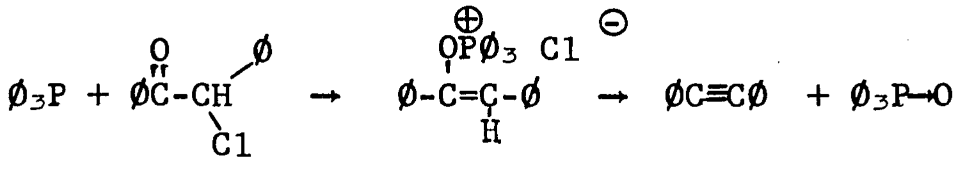
Strong support for this viewpoint was the isolation of the enol phosphonium salt (XLII) from the reaction of triphenylphosphine with α,α-diphenyl-α-chloroacetophenone (XLI).(22) Hydrolysis of XLII led to the dehalogenated ketone (XLIII) and triphenylphosphine oxide and pyrolysis at 195° (0.2 mm.) gave the expected product of the halogen migration reaction, triphenylchloroethylene (XLIV).



XLII is reported to be an extremely hygroscopic white solid.

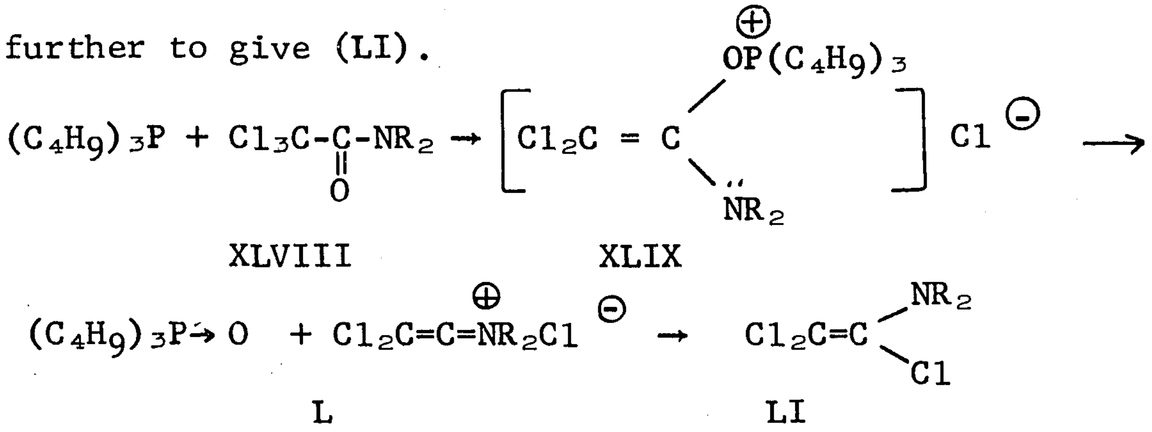
Desyl chloride (XLV) reacts with triphenylphosphine in refluxing benzene to yield diphenylacetylene (XLVII).(9)

It has been proposed(16,17,21) that the reaction goes via the enol phosphonium salt (XLVI).



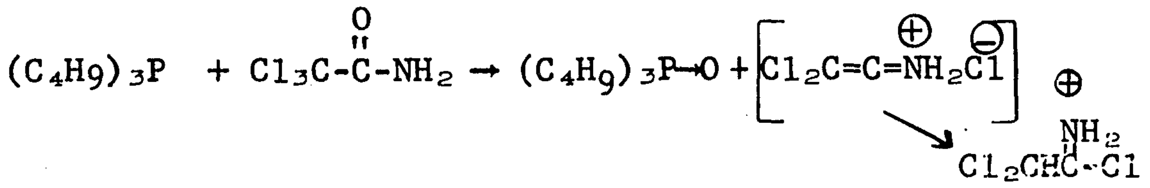
XLV XLVI XLVII

Speziale and co-workers(8,23) investigated in detail the reaction of chlorocarboxamides with phosphines and found that an initial step similar to that involved in the formation of enol phosphonium salts was followed by the replacement of the phosphinoxy group by chlorine. Thus, N,N-disubstituted trichloroacetamides (XLVIII) react with tributylphosphine to yield trichlorovinylamines LI in excellent yields. Presumably the enol phosphonium XLIX is obtained, but dissociates spontaneously to form a ketiminium salt L which then reacts further to give (LI).



XLVIII XLIX L LI

When trichloroacetamides bear at least one hydrogen on the nitrogen atom, imidoyl chlorides (LII) are obtained(8) instead of the tautomeric vinyl amines.

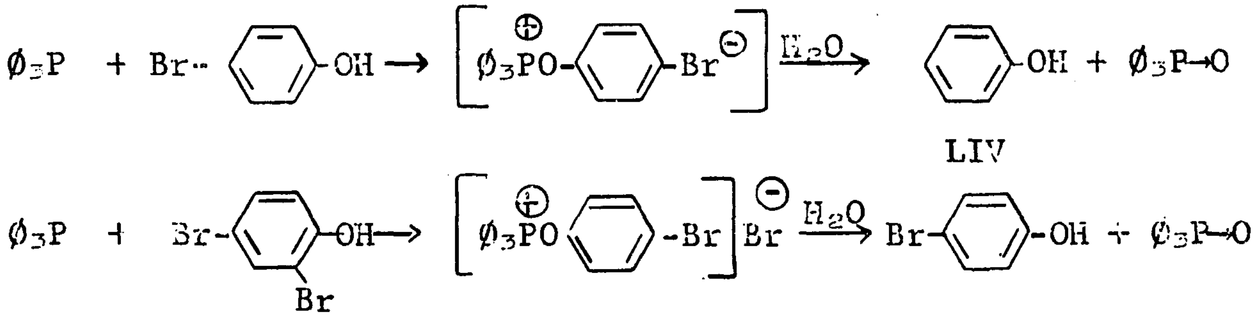


$$(C_4H_9)_3P + Cl_3C-\overset{O}{\overset{\|}{C}}-NH_2 \rightarrow (C_4H_9)_3P\rightarrow O + \left[Cl_2C{=}C{=}\overset{\oplus}{N}H_2\overset{\ominus}{Cl}\right] \searrow Cl_2CHC{\overset{\overset{\oplus}{N}H_2}{\|}}-Cl$$

LII

Arylated dichloroacetamides similarly give good yields of dichlorovinylamines, but other dichloroacetamides react only slowly or form C-phosphonium salts.

Hoffmann and his co-workers(24) found that o- and p-bromo- or iodophenols react with tertiary phosphines in inert solvents or in the melt to give aryloxyphosphonium salts, e.g.LIII, which are immediately hydrolyzed to triphenylphosphine oxide and the dehalogenated phenol. Thus, triphenylphosphine reacts with p-bromophenol to yield phenol LIV and removes the ortho halogen from phenol LV. Chloro-

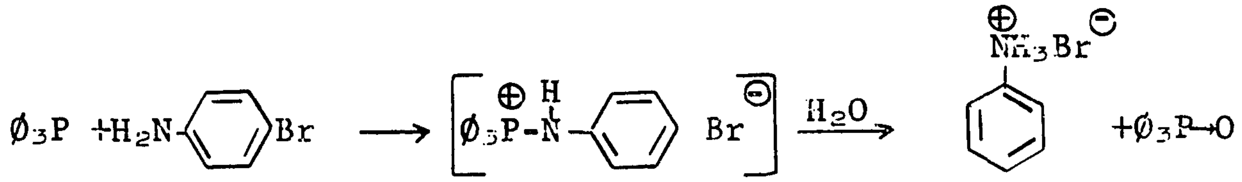


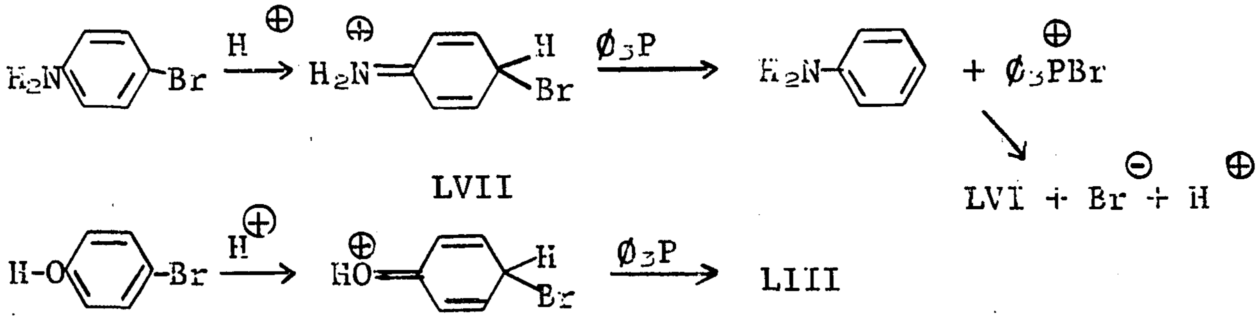
LIV

LV

phenols, however, are reported to be unreactive.

p-Bromoaniline reacts with triphenylphosphine in a similar manner, forming a phosphinimidium salt (LVI) which is instantly hydrolyzed by water.(25) It was found(25) that the reaction of such brominated arylamines is catalyzed by traces of acids and inhibited by aliphatic amines. The reaction mechanism suggested is initial addition of a proton to give a bromocyclohexadieniminium salt, e.g. LVII, from which a bromine cation is then removed by the phosphine. The debromination of phenols is believed to proceed similarly.


LVI


LVII

RESULTS AND DISCUSSION

α-Haloketones react with tertiary phosphines to give α-ketophosphonium salts ("C-phosphonium salts")$^{(26)}$ or, alternatively, enol phosphonium salts ("O-phosphonium salts").$^{(16,17,21,22)}$ The mechanisms proposed for these reactions include initial attack of phosphorus on oxygen to give enol phosphonium salts directly,$^{(21)}$ or attack on the halogen to give an enolate bromophosphonium ion pair which is then converted to enol phosphonium salts.$^{(8,16,17)}$ The formation of α-ketophosphonium salts has been postulated to occur either by straightforward displacement$^{(27)}$ or by rearrangement of enol phosphonium salts.$^{(28)}$

To aid our understanding of the factors involved in the formation of either ketophosphonium or enol phosphonium salts, the reaction of triphenylphosphine with a series of α-haloketones was studied under a variety of conditions.

In Table I are summarized the results for the reaction of phenacyl bromide with triphenylphosphine. The main feature to be noted is the great reduction in the yield of phenacyltriphenylphosphonium bromide (LXI), which is stable to refluxing methanol,(16) and the corresponding increase in the yield of acetophenone (LX) brought about by the initial addition of methanol to the reaction mixture of bromoketone and phosphine. This result suggests that the apparently straightforward displacement of bromide ion by triphenylphosphine actually must involve one or more intermediates prior to the formation of the known(26) phosphonium bromide (LXI). Two possible mechanisms are presented in Figure 1. Path (a) involves the direct formation of the enol phosphonium salt (LIX) in benzene by attack of the phosphorus on the oxygen of phenacyl bromide (LVIII) and a subsequent rearrangement to the α-ketophosphonium salt LXI; path (b) visualizes a displacement on the bromine of LVIII to give an enolate bromophosphonium ion pair (LIXa) which then can go either to the O-phosphonium salt LIX or the C-phosphonium salt LXI.

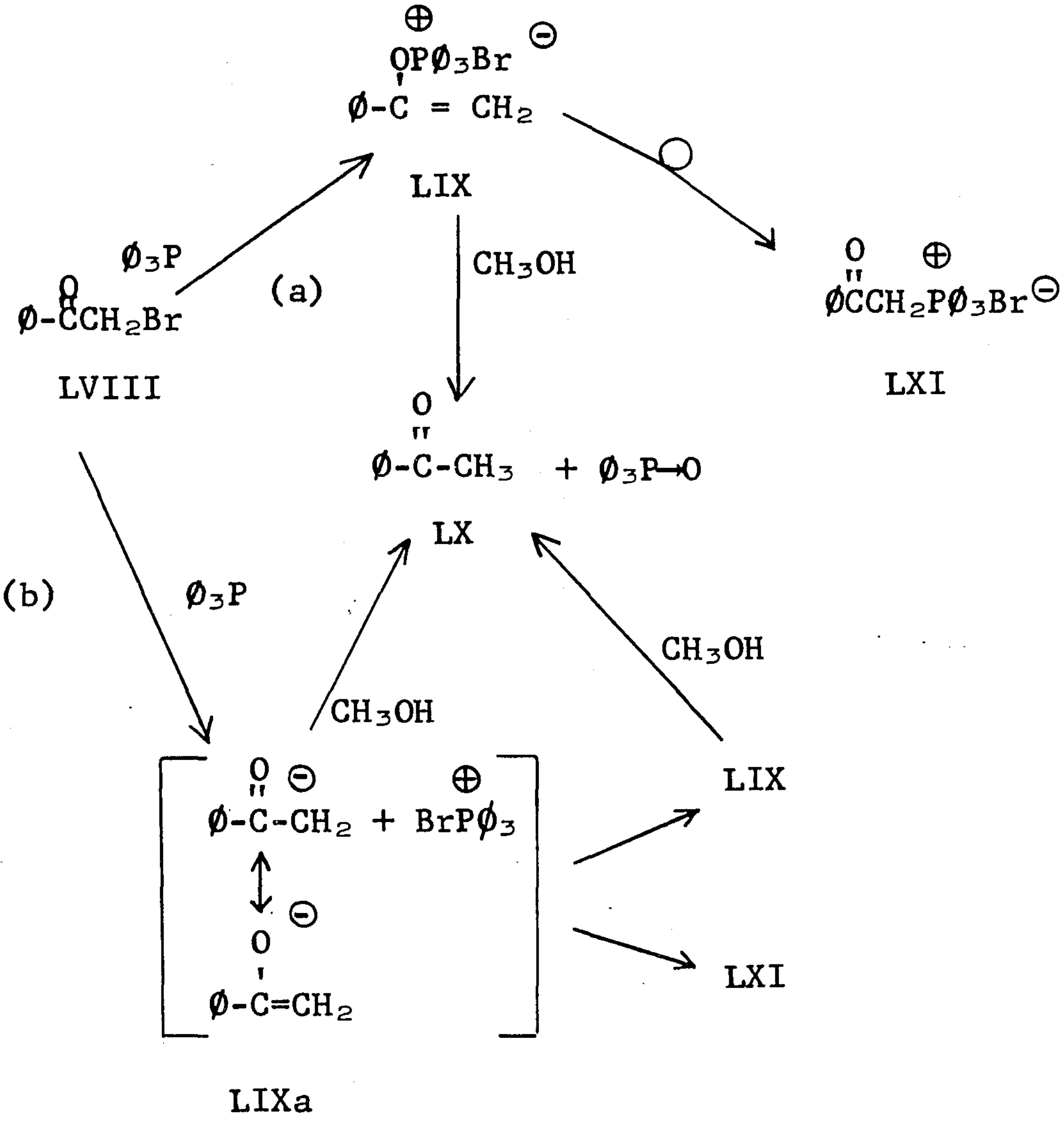


Figure 1

Table I

Reaction of Phenacyl Bromide with Triphenylphosphine:(a)

Reaction Conditions:	Yields, %		
	$\overset{+}{CP}$ LXI	$\emptyset C\overset{O}{=}CH_3$	$\emptyset_3PO$
In refluxing benzene	80	6(c)	19
In refluxing benzene with excess methanol added	9	50,(c) 88(g)	92
In refluxing benzene with 1.45 eq. methanol added	12	86(c)	54
In refluxing acetonitrile with 4 eq. dimedone added	67	34(d)	ca. 27(h)
In diethylmalonate at 123°	62	(e)	19
In diethylmalonate at 25°	80		
In ethylcyanoacetate-benzene at 25°	95		
In ethylcyanoacetate-acetonitrile at 25°	88		
In malononitrile at 95°	82	(f)	

(a) All products gave satisfactory infrared spectra or melting points and were compared to genuine samples by thin layer chromatography (TLC). (b) All are isolated yields. (c) Yield based on conversion to the 2,4-dinitrophenylhydrazone. (d) Determined by NMR; a 19% yield of 5,5-dimethyl-3-bromocyclohexenone(XXXII) was also obtained. (e) Refer to the discussion (f) Detected by TLC. (g) Determined by v.p.c. (h) Contained dimedone.

In path (a) the formation of LX is interpreted as due to the solvolysis of the enol phosphonium salt LIX and in path (b) it is looked upon as an indication of the protonation of the enolate ion in LIXa.

A third possible mechanism, which seems to be the least likely, visualizes the active participation of the alcohol in the reaction (Figure 1a).

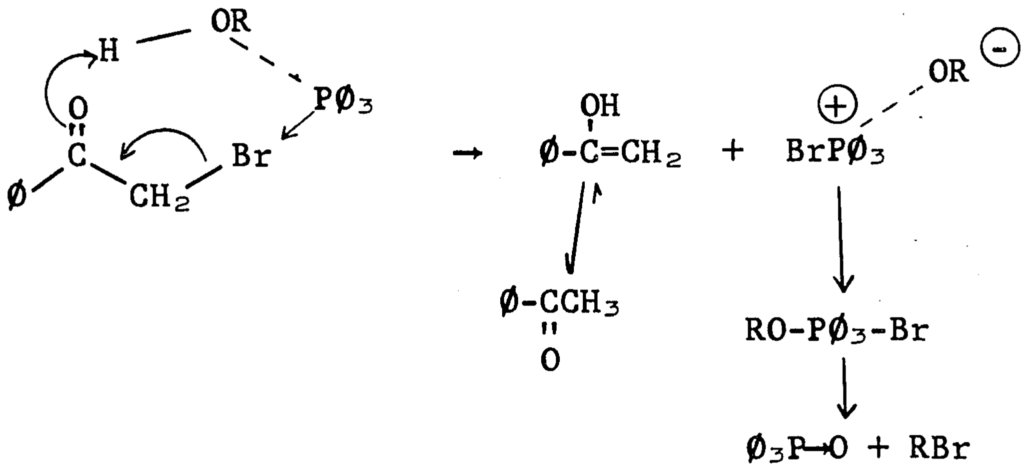


Figure 1 a

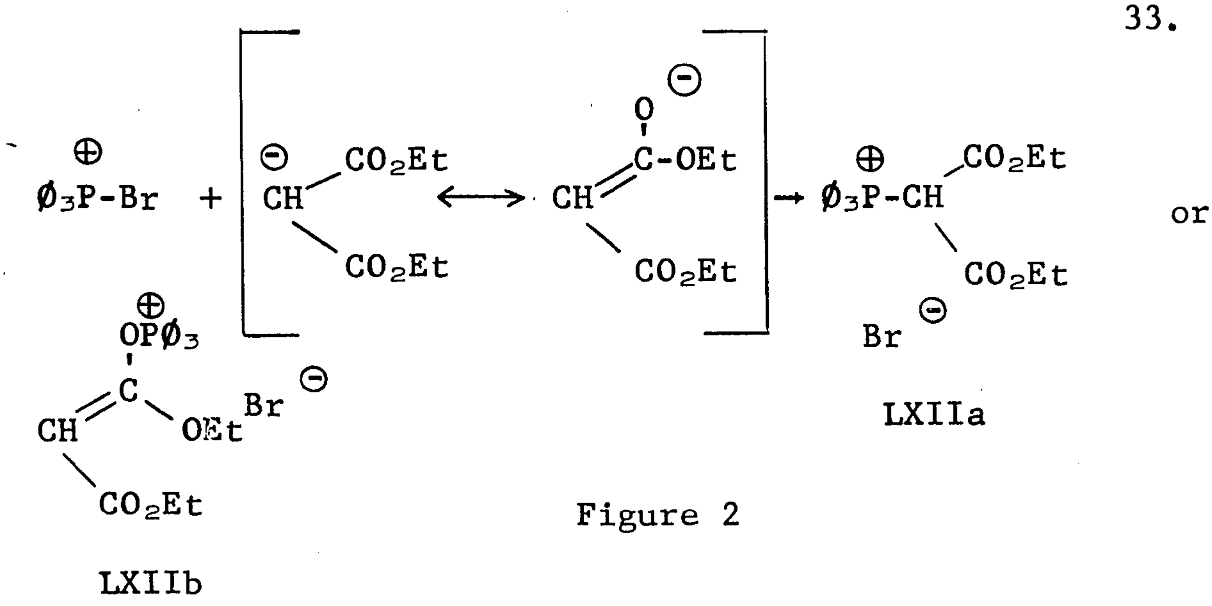
It was decided that a possible way of differentiating between these reaction paths was to perform the reaction in the presence of compounds which are sufficiently acidic to protonate the ion-pair LXIa but cannot decompose the enophosphonium salt once it has been formed. Any lowering in the yield of the phosphonium salt LXI together with an increase in the amount of debrominated product LX under these circumstances would then provide evidence for the presence of the enolate bromophosphonium pair LIXa at some stage of the reaction and would, therefore, lend support to path (b) in Figure 1. The results of these experiments are also presented in Table I. It can be seen that a small reduction in the yield of the phosphonium salt LXI was achieved only in hot diethylmalonate and in the presence of dimedone.

Before the significance of these two results is discussed, it should be mentioned that many difficulties were encountered in the use of diethylmalonate. The commercial product contained appreciable quantities (1-2%) of ethanol whose presence was not detected initially. Therefore, early runs of the reaction of phenacyl bromide with triphenylphosphine in diethylmalonate, performed on a 4-6 mmoles scale, gave only a 35% yield of the phosphonium salt LXI and as high as 61% yield of LX.(29) Repeated distillation of the diethylmalonate from calcium hydride through a 23 cm. vacuum-jacketed silvered Vigreux column finally gave material which was pure by v.p.c. However, it was essential to keep the injector and column temperature below 150° for otherwise partial decomposition of the diethylmalonate occurred, giving ethanol as one of the products.

The reaction of LVIII with triphenylphosphine in hot diethylmalonate for 6.5 hrs. gave a decreased yield of the phosphonium bromide LXI. Acetophenone (LX) was detected by thin layer chromatography (TLC). Distillation at reduced pressure gave a colorless liquid which by calculation could have contained only 0.6% of acetophenone by weight. By flooding a column of 20% Carbowax with the diethylmalonate solution, a small symmetrical peak for acetophenone was obtained whose area by comparison to a calibration curve represented less than 1% of the total weight of material injected on the column. Thus, although the maximum amount of LX (i.e. $>$ 30% yield) had apparently been obtained, no value is entered in Table I because of the very large error involved in the determination.

As controls, a mixture of LVIII and diethylmalonate after being heated for 24 hrs., and a mixture of triphenylphosphine and diethylmalonate after being heated for 25.5 hrs., gave no other compounds as determined by TLC. Similarly, when a suspension of LXI in hot diethylmalonate was rapidly stirred for 21 hrs., no decomposition was detected and the recovery of LXI was nearly quantitative.

Since all of these control solutions remained light yellow, the evident charring (dark brown color) observed in the actual reaction of LVIII with triphenylphosphine in hot diethylmalonate might be due to the decomposition of the non-isolable phosphonium bromide LXII, which could have been formed from the combination of the malonate anion with the bromotriphenylphosphonium cation. (Figure 2) Neither LXIIa or LXIIb has ever been actually isolated. It has been reported(17) that bromomalonate and triphenylphosphine react to give an "adduct" which was postulated to be the enol phosphonium salt LXIIb on the basis of its facile solvolysis to diethylmalonate and triphenylphosphine oxide. However, it appears equally probable that the



LXIIa

LXIIb

Figure 2

unstable "adduct" is in reality the C-phosphonium salt LXIIa, since it is known(30) that the addition of 2 equivalents of triethylamine to the reaction of bromomalonate with triphenylphosphine in refluxing benzene yields the stable ylide.(Figure 3)

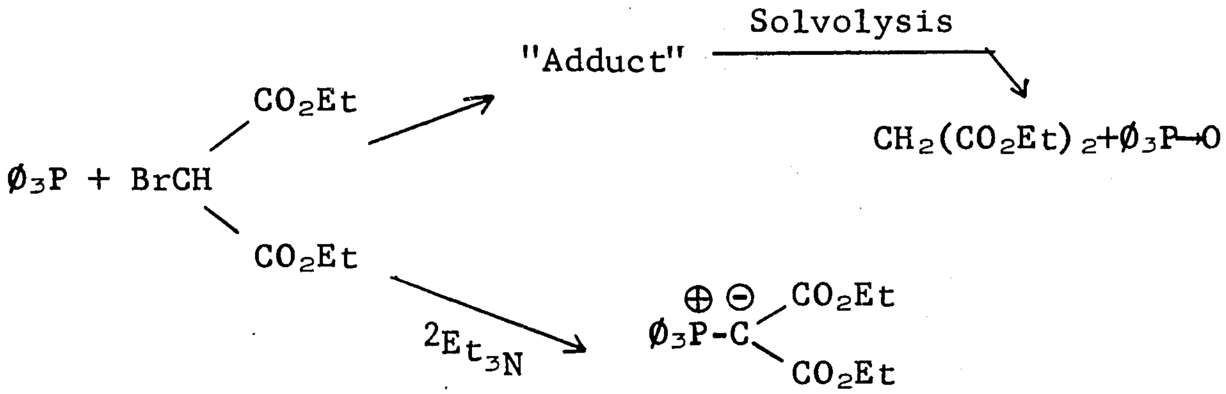


Figure 3

The yield of the phosphonium salt LXI was also reduced in the presence of dimedone (5,5-dimethyl-cyclohexane-1,3-dione) (LXIII) and yield of LX was increased. (Refer to Table I). However, this result does not allow a differentiation of paths (a) or (b) in Figure 1, because LXIII can not only protonate the enolate ion in LIXa but can also solvolyze the postulated intermediate enol phosphonium salt LIX as does methanol. The formation of the bromoeneone XXXII (identified by comparison with authentic spectra available in this laboratory) can be explained as the result of the bromination of an enolic form of LXIII by a bromophosphonium species. (Figure 4) (LXIII exists, for instance, as an equilibrium of the keto form LXIIIa and the enolic dimer LXIIIb in chloroform solution).(31) Thus LXIII is known to react with phosphorus tribromide to give XXXII.(22)

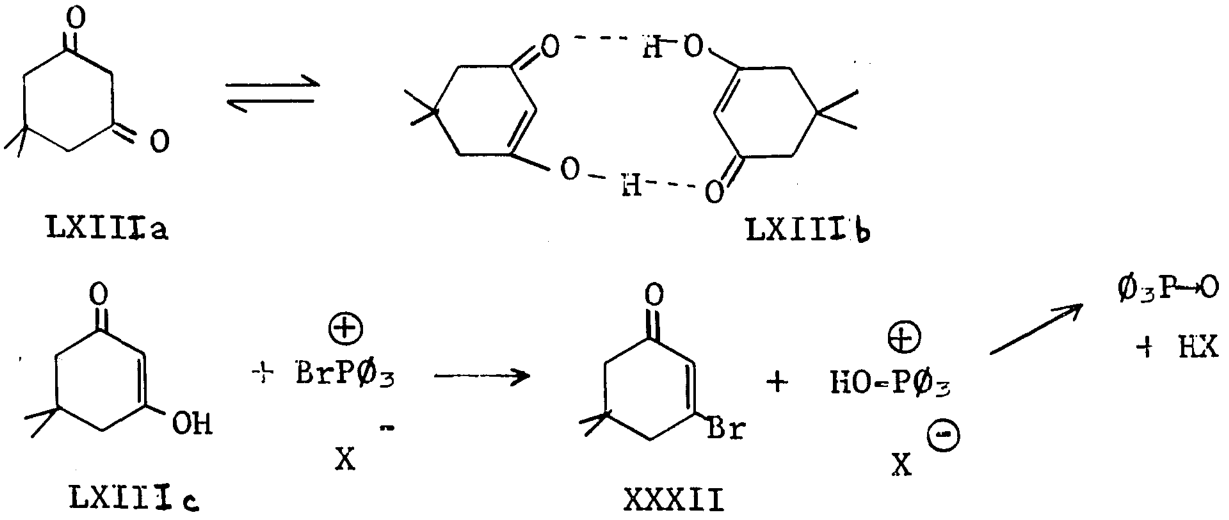


Figure 4

The yield of XXXII and acetophenone (LX) was most conveniently determined by NMR (neat) by integration of the respective CH_3-peak areas at 0.97 δ (singlet) and 2.48 δ (singlet).

Since little or no interception was achieved by the addition of such compounds as are listed in Table I to the reaction mixture of phenacyl bromide and triphenylphosphine, it appears that this method is not sensitive enough to detect the transitory presence of an enolate ion. Perhaps, also, the enolate is so tightly bound in the ion-pair LIXa that it reacts internally rather than undergoes external protonation.

Various alkylations were also attempted as a means of detecting the presence of an enolate ion. (See Figure 5) These were uniformly unsuccessful since a high yield of LXI was obtained in each instance. Thus, no LXV was detected in the slow inverse addition of triphenylphosphine to a solution of phenacyl bromide in diethylmalonate. When n-butyl iodide was added to the reaction mixture, it merely competed to alkylate the phosphine and a mixture of n-butyl and phenacyl phosphonium salts was obtained. No alkylated ketone LXVI was detected by thin layer chromatography.

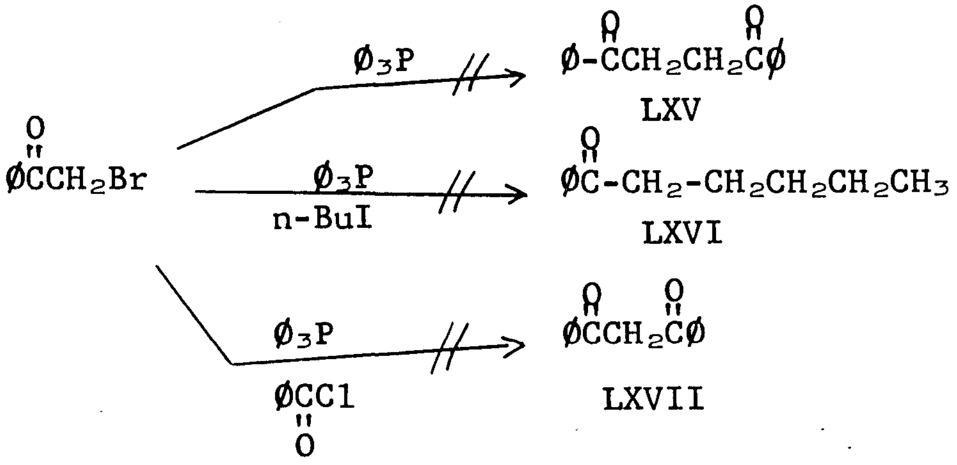


Figure 5

Lastly, the attempted acylation with benzoyl chloride gave no dibenzoylmethane (LXVII) as determined by thin layer chromatography. However, it is reported by Weygand(33) that thiolate ions react with α-bromoketones in the following manner: (Figure 6).

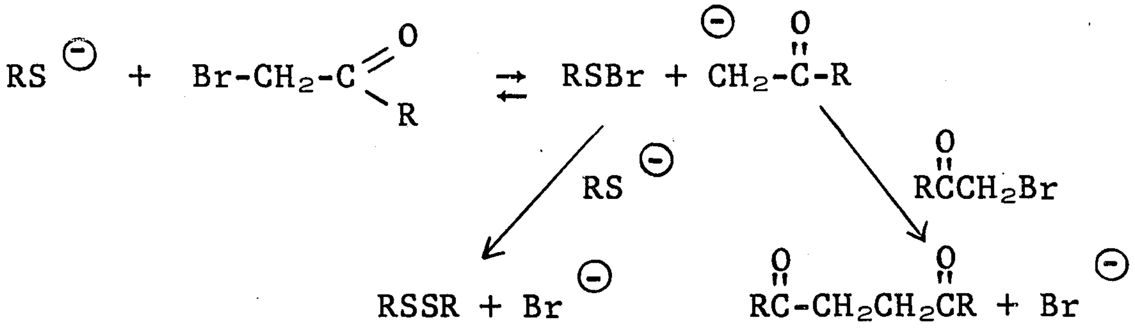


Figure 6

It should be noted that the initial formation of the enolate ion is postulated to be a reversible process. If this were the case in the reaction of phenacyl bromide with triphenylphosphine, interception by excess phenacyl bromide and diethylmalonate should have occurred. It is therefore suggested that the haloketone triphenylphosphine reaction is not reversible. It should be noted that two enol phosphonium salts have been isolated and that they do not revert to the starting compounds.(17,22)

In contrast to the results obtained with phenacyl bromide, the formation of neither acetonyltriphenylphosphonium chloride (LXVIII) nor phenacyltriphenylphosphonium chloride (LXIX) was affected by the initial presence of excess methanol. The data are summarized in TablesII and III. It appears, therefore, that both of these chlorides react with triphenylphosphine primarily by straightforward displacement of chloride ion.

Table II

Reaction of α-Chloroacetone with Triphenylphosphine

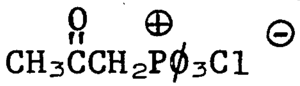
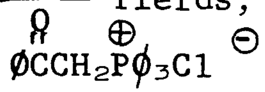
Reaction Conditions:	Yields, %		
	 $CH_3\overset{\overset{O}{\|}}{C}CH_2\overset{\oplus}{P}\phi_3\overset{\ominus}{Cl}$ LXVIII	$\phi_3P\rightarrow O$	ϕ_3P
In refluxing benzene-acetonitrile	84	5	11
In refluxing acetonitrile with excess methanol added	86	6	6

Table III

Reaction of Phenacyl Chloride with Triphenylphosphine

Reaction Conditions:	Yields, %
	 $\phi\overset{\overset{O}{\|}}{C}CH_2\overset{\oplus}{P}\phi_3\overset{\ominus}{Cl}$ LXIX
In refluxing benzene, 24 hrs.	93
In refluxing benzene with excess methanol added, 24 hrs.	95

Attention was next focused on the alkylated members of the acetophenone series and the reactions of α-bromo-propiophenone, -isobutyrophenone, and -deoxybenzoin with triphenylphosphine were studied. Before discussing each of these reactions in detail, individually, certain broad similarities detected in this series of compounds can first be mentioned. The initial addition of excess methanol, in each of these cases, completely prevented the formation of the C-phosphonium salt and gave instead the debrominated ketone in high yield. The data are presented in Tables IV, VI and VII. Since each of the C-phosphonium bromides, i.e., LXX, LXXI and LXXII, once formed, is stable to refluxing methanol, the interception by methanol must occur at an intermediate stage in each of the reactions, indicating again that the formation of these C-phosphonium salts is probably a multi-step process. Reaction pathways similar to those depicted in Figure 1 for phenacyl bromide can again be invoked.

No reduction in the yields of the C-phosphonium salts LXX, LXXI and LXXII was obtained in the presence of the proton-donor diethylmalonate. This result again points to the difficulty in obtaining evidence for intermediate enolate formation in these reactions. Namely, the diethylmalonate always competes for the enolate ion with the closer and more reactive species: bromotriphenylphosphonium ion. The latter may very well be associated with the enolate as a very tightly bound ion-pair, c.f. LIXa. In the α-bromopropiophenone and α-bromoisobutyrophenone cases, moreover, the derived enolates, being more substituted carbanions, are presumably both more reactive than the anion of acetophenone, and hence more difficult to trap. They are also possibly more hindered towards external protonation. In view of such considerations, it is perhaps not difficult to understand why diethylmalonate failed to intercept the formation of these C-phosphonium salts.

In non-hydroxylic solvents, α-bromopropiophenone (LXXIII) reacted with triphenylphosphine to give the expected α-methylphenacyltriphenylphosphonium bromide (LXX). (See Table IV).

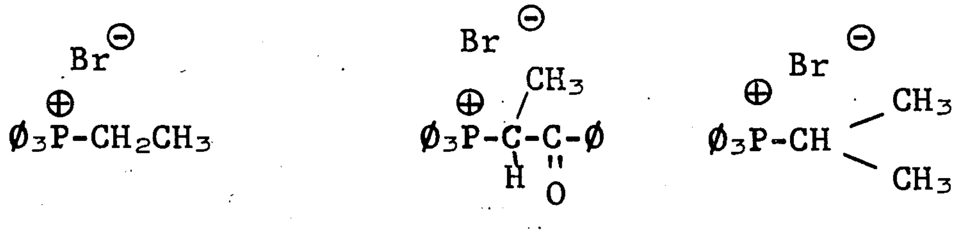
Table IV

Reaction of α-Bromopropiophenone with Triphenylphosphine[a]

Reaction Conditions:	Yields, %			
	$\overset{+}{\text{CP}}$ LXX	$\phi\overset{O}{\overset{\|}{C}}\overset{Br}{C}H-CH_3$	$\phi\overset{O}{\overset{\|}{C}}CH_2CH_3$	ϕ_3PO
In refluxing benzene, 1.5 hrs.	24	18(b)	52(b)	80(b,c)
In refluxing benzene, 10 hrs.	62	-	-	-
In refluxing benzene, 17 hrs.	73	-	-	-
In refluxing benzene, 21 hrs.	78	9(b)	18(b)	ca. 27(b)
In refluxing benzene, 31 hrs.	83	9(b)	13(b)	ca. 22(b)
In refluxing benzene with excess methanol added	-(d)	32(e)	70(e)	60
In refluxing benzene with excess diethylmalonate, at 85°, 30 hrs.	67		23(e)	
In refluxing acetonitrile	81		14(f)	20

(a) All products gave satisfactory analyses or infrared spectra or melting points and were compared to genuine samples by thin layer chromatography (TLC). (b) Determined by quantitative TLC. (c) Isolated yield was 65%. (d) Methyltriphenylphosphonium bromide was obtained in 33% yield. (e) Determined by v.p.c. (f) Determined by NMR.

The NMR spectrum ($CDCl_3$) of LXX shows signals for aromatic hydrogens at 7.17-8.81 δ (relative intensity 20.0) and a quartet of peaks, centered at 1.84 δ, for the α-methyl group (relative area 2.6) with J_{HCCH} = 7.5 cps and J_{PCCH} = 19 cps. The assigned coupling constants are of the same magnitude as similar J-values determined by Griffin(34) for ethyl- and isopropyltriphenylphosphonium bromides. (Figure 7). Because of the low solubility of LXX in the organic solvents commonly used in NMR, the α-proton signal (octet) was lost in the "noisy" baseline.



$\overset{\oplus}{\phi_3P}-CH_2CH_3 \quad Br^{\ominus}$

$\phi_3\overset{\oplus}{P}-\underset{H}{\overset{CH_3}{C}}-\underset{O}{\overset{\|}{C}}-\phi \quad Br^{\ominus}$

$\phi_3\overset{\oplus}{P}-CH(CH_3)_2 \quad Br^{\ominus}$

LXX

J_{HCCH} = 7.5 J_{HCCH} = 6.9

J_{PCCH} = 20.0 J_{PCCH} =18.7

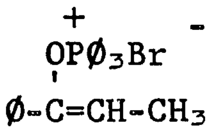
Figure 7.

LXXIII reacted slowly with triphenylphosphine in refluxing benzene. Thus, a 24% yield of LXX was obtained in 1.5 hrs., and the maximum yield (83%) of LXX was achieved only after a reaction time of 31 hrs. (Refer to Table IV). In order to find out whether the slow formation of LXX could be explained by a slow disappearance of LXXIII, at least a rough estimate was needed of the amount of unreacted LXXIII present after a given period of time.

At the time of the initial consideration of this problem, a survey of the available instrumentation suggested the use of quantitative thin layer chromatography(35) for the analysis of the product mixtures. The exact technique which was used is described in the Experimental section. However, in general, the benzene-insoluble LXX was removed by filtration. Since at this point a white solid (which fumed in air and gave via TLC a large spot for triphenylphosphine oxide and a smaller spot for triphenylphosphine) usually precipitated from the clear benzene filtrate, it became necessary to add methanol in order to achieve a homogeneous solution. After fractional distillation and isolation of the bulk of the triphenylphosphine oxide, the residual solution was spotted on a Silica Gel HF_{254} plate. After development, the components of the mixture were located with ultraviolet light and the appropriate areas of adsorbentwere scraped off the plate and were extracted with 95% ethanol. The yield of each component was then determined spectrophotometrically. Although such a method is reported to give the most accurate results,(35) it can be appreciated that each of the above manipulations is a possible source of error, especially in the case of volatile components. It is estimated, therefore, that the values which were determined in this manner have an accuracy of about ±4%.

The quantitative TLC indicated that the major product in the reaction mixture at the end of 1.5 hrs. refluxing in benzene was propiophenone. The amount of unreacted α-bromopropiophenone detected corresponded to only an 18% recovery. (Refer to the data in Table IV). This result was most surprising since on the basis of the knowledge that the yield of LXX increases slowly with increasing refluxing time it was expected that most (i.e. 76%) of the α-bromopropiophenone (LXXIII) would be recovered unchanged when the reaction was terminated at the end of 1.5 hrs. The high yield of the debrominated ketone seemed to suggest (1) that LXXIII had reacted much more rapidly and more completely than was indicated by the isolation of the phosphonium salt LXX and (2) that perhaps LXX was in reality the rearrangement product of an initially formed enolphosphonium salt LXXIV and the propiophenone the hydrolysis product.

However, another possible explanation of the results was suggested by a consideration of the reaction work-up.



$$\begin{array}{c} \overset{+}{\text{O}}\text{P}\phi_3\text{Br}^{-} \\ | \\ \phi\text{-C=CH-CH}_3 \end{array}$$

LXXIV

Namely, perhaps the propiophenone was in reality the end-product of secondary reactions which had been initiated or accelerated by the addition of methanol to the reaction mixture of LXXIII and triphenylphosphine in benzene.

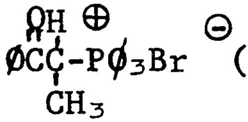
To test the validity of the quantitative TLC procedure, it was decided to determine the amount of unreacted LXXIII also by a potentiometric titration of bromide ion. Such a method would avoid the necessity of adding methanol.

Therefore, after a given period of time, water was injected directly into the reaction mixture through a rubber septum attached to one of the necks of the reaction flask. After the insoluble LXX had been collected by filtration, the benzene and water layers were carefully separated and diluted to known volumes. An aliquot of the strongly acidic aqueous layer was directly titrated with 0.0500 N silver nitrate solution and the end point was determined potentiometrically. An aliquot of the benzene layer was first refluxed with 20% aqueous sodium hydroxide solution. After acidification with 1:1 nitric acid, the aliquot was titrated with silver nitrate solution. The data obtained in this manner are presented in Table V.

In the control experiment, LXXIII was refluxed in benzene for 2 hrs. after which 0.16 M aqueous nitric acid was injected through the septum attached to a neck of the reaction flask. The rest of the procedure was as already described. It was found that only traces of ionic bromine were present in the water layer while 97% of the total bromine used was detected as bromide ion in the benzene layer.

Table V

Potentiometric Titration of Bromide Ion in the Reaction of α-Bromopropiophenone with Triphenylphosphine

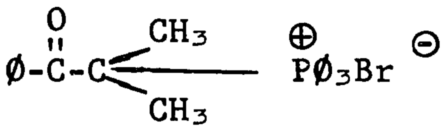
Reaction Conditions:	Yields, %			
	 $\phi\overset{O}{\overset{\|}{C}}\underset{CH_3}{\overset{H}{C}}-\overset{\oplus}{P}\phi_3\overset{\ominus}{Br}$ (LXX)	$\overset{\ominus}{Br}$ in ϕH Layer	$\overset{\ominus}{Br}$ in H_2O Layer	Total $\overset{\ominus}{Br}$ Detected
In refluxing benzene, 2 hrs.	29	40	25	94
In refluxing benzene, 10 hrs.	69	19	7	95

The success of this potentiometric titration method obviously depended on the assumptions: (1) that the reaction in progress was immediately terminated by the addition of water and that no new reactions were initiated and (2) that all bromine containing phosphonium species, other than LXX and LXXIII, were destroyed and the liberated bromide ion was extracted completely into the water layer.

From the data in Table V it should be noted that at the end of 2 hrs. of reaction, 40% of the total bromine was detected as bromide ion in the benzene layer. The suggested yield of unreacted LXXIII, therefore, is approximately twice as great as that obtained by the addition of methanol and determination of the products by quantitative TLC. The validity of the latter determination, therefore, apparently is truly questionable. However, the finding that 25% of the bromine appeared as bromide ion in the water layer is disturbing because this result again suggests that more LXXIII has actually reacted than is revealed by the isolation of the phosphonium salt LXX. The possibility that the addition of water did not quench all possible reactions in the α-bromopropiophenone-triphenylphosphine mixture cannot, of course, be neglected.

Therefore, in summary, until the development of a more elaborate method allows a precise determination of the amount of unreacted α-bromopropiophenone in the benzene reaction mixtures, an unequivocal statement of the manner of formation of LXX cannot be formulated.

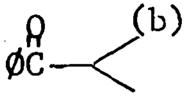
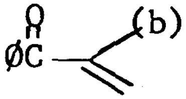
The data from the reaction of α-bromoisobutyrophenone with triphenylphosphine are summarized in Table VI. It should be noted that the expected α, α-dimethylphenacyltriphenylphosphonium bromide (LXXV) was not formed under any of the conditions listed. Instead, the phosphonium bromide LXXI was isolated. The structure of LXXI was proved by synthesis using the sequence of reactions depicted in



LXXV

Table VI

Reaction of α-Bromoisobutyrophenone with Triphenylphosphine (a)

Reaction Conditions:	Yields, %			
	$\overset{+}{\text{CP}}$ LXXI	 (b)	 (b)	ϕ_3PO (e)
In refluxing benzene, 24hrs.	0	68	21	89 (f)
In refluxing benzene with excess methanol added	0 (c)	65	12	83
In refluxing benzene with excess methanol added and 2.3 eq. triphenylphosphine	0 (d)	97	-	45
In diethylmalonate at 110°	45	32	-	39
In refluxing acetonitrile, 20.5 hrs.	48	29	13	ca. 52

(a) All products gave satisfactory analyses or infrared spectra or melting points and were compared to genuine samples by thin layer chromatography.
(b) Determined by NMR. (c) Methyltriphenylphosphonium bromide was obtained in 13% yield. (d) Methyltriphenylphosphonium bromide was obtained in 38% yield. (e) All are isolated yields. (f) Includes 39% of hydroxytriphenylphosphonium bromide.

Figure 8. α-Bromoisobutyrophenone was converted to α-methacrylophenone (LXXVI) in 50% yield according to the procedure

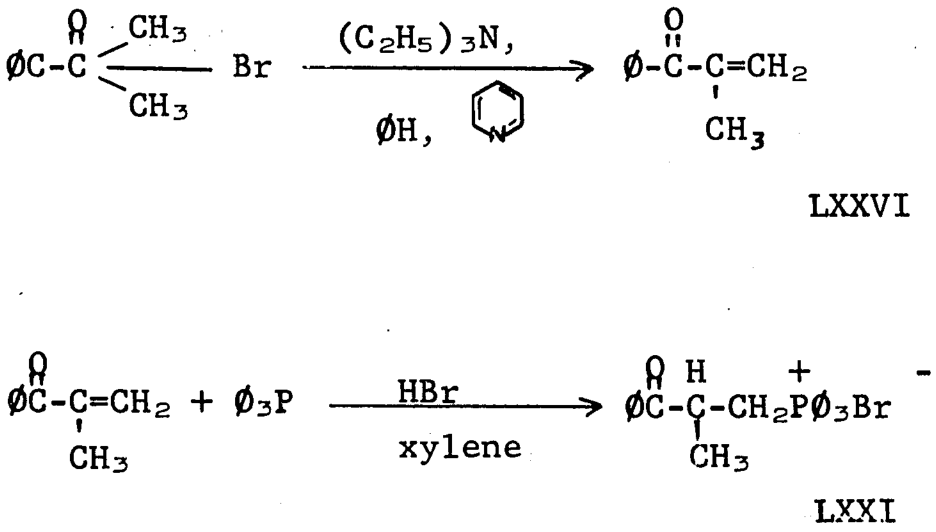
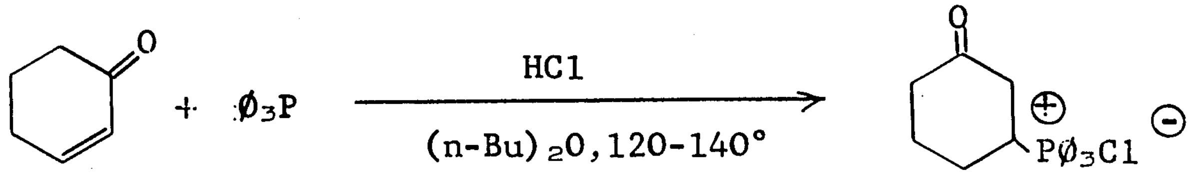


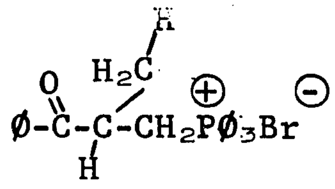
Figure 8

of Stevens and Ettling.(33) LXXVI then reacted with triphenylphosphine in the presence of anhydrous hydrogen bromide to give LXXI in 79% yield. A similar reaction has been very recently reported by Chopard and co-workers(37) who bubbled a slow stream of hydrogen chloride through a solution of triphenylphosphine and cyclohexene-2-one in hot di-n-butylether and obtained β-ketocyclohexylphosphonium chloride (LXXVII).

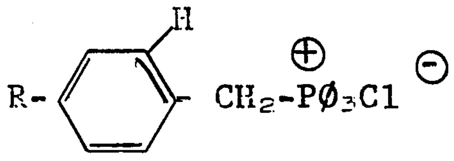


LXXVII

The structure of LXXI was fully substantiated by its proton NMR spectrum ($CDCl_3$) which gave a complex band at 7-8.0 δ (relative intensity 20.6), a broad series of signals near 4.0 δ (relative intensity 3.3), and a split doublet centered at 1.65 δ (relative intensity 3.0). These bands are assigned respectively to the phenyl, methine and methylene, and methyl protons. Scale expansion revealed that the CH_3- group shows as a doublet of doublets (rather broad) with J=6.4, 2.3. The large coupling is J_{HH}, and the smaller coupling apparently is J_{PH}. Thus, Griffin(34) has studied the proton NMR spectra of p-nitrobenzyltriphenylphosphonium and p-methylbenzyltri-n-butylphosphonium chlorides LXXVIII and has observed a four-bond coupling of the phosphorus atom with the ring protons ortho to the methylene group with magnitudes of 2.3 and 2.2 cps. respectively.



LXXI



(R=CH_3-,NO_2-) LXXVIII

In an attempt to eliminate the possibility that LXXV was not isolated because it is unstable at refluxing temperatures, the reaction of α-bromoisobutyrophenone with triphenylphosphine was performed at room temperature (ca. 25°) in acetonitrile in the hope of detecting LXXV by NMR. Space-filling Fisher-Hershfelder models seemed to indicate that the two CH_3- groups of LXXV may not be equivalent because of hindered rotation. Therefore, two different CH_3- proton signals might be observed. Further coupling with P^{31} should split each of these signals in two to yield a total of four lines for the CH_3- groups of LXXV in the proton NMR spectrum.

Unfortunately, at the end of 43 hrs. stirring at room temperature, apparently only little reaction between α-bromoisobutyrophenone and triphenylphosphine had occurred.

A fuming material was isolated which was thought to be a complex salt of triphenylphosphine-triphenylphosphine oxide on the basis of its hydrolysis to triphenylphosphine oxide on a TLC plate. The ketonic fraction contained only α-bromoisobutyrophenone and isobutyrophenone in the ratio of 78:22 (by NMR in carbon tetrachloride). No LXXVI was detected.

It should be stated at this point that LXXVI could not be separated from isobutyrophenone by TLC on Silica Gel HF_{254} plates. On various v.p.c. columns tried, e.g. 20% Carbowax, 20%SE-30, LXXVI appeared as an unresolvable shoulder on the isobutyrophenone peak. However, mixtures containing LXXVI could be analyzed by NMR from the intensity of the respective CH_3- proton signals. Thus, the methyl group of LXXVI showed as a singlet at 2.0 δ, the methyl groups of α-bromoisobutyrophenone appeared as a singlet at 1.93 δ and the methyl groups of isobutyrophenone produced a doublet centered at 1.12 δ.

When the reaction period at room temperature was extended to 96 hrs., in acetonitrile, a hygroscopic powder was obtained which was placed directly into an NMR tube containing deuterochloroform. The spectrum showed a large complex multiplet at 7.4-8.0 δ(phenyl absorption) and a small multiplet centered at 1.6 δ (CH_3-of LXXI). However, in addition, there was a previously unseen quintet at 1.05-1.30δ. Of the identified products, only the methyl signals (doublet) of isobutyrophenone are found in this region. It was unlikely, however, that four of these peaks could be due to LXXV. The methyl protons of LXXV are deshielded by both the carbonyl group and by the phosphorus atom. Therefore, the methyl signal should appear downfield from 1.5 δ (c.f.LXXI). On this basis, the quintet observed must remain unassigned.

The multiplets centered at 1.6 and 1.18 δ , however, were both very small when compared to the phenyl absorption at 7.4-8.0 δ . Therefore, apparently the major portion of the hygroscopic powder was again a complex salt of triphenylphosphine-triphenylphosphine oxide. The only ketonic products detected at the end of 96 hrs. were α -bromoisobutyrophenone and isobutyrophenone in a 62:38 ratio by NMR (CCl_4).

These results indicate that a synthesis of the unknown LXXV must be attempted in a different way. Perhaps the method of Bestmann(38), illustrated in Figure 9, can be successfully extended to a more substituted ylide to yield

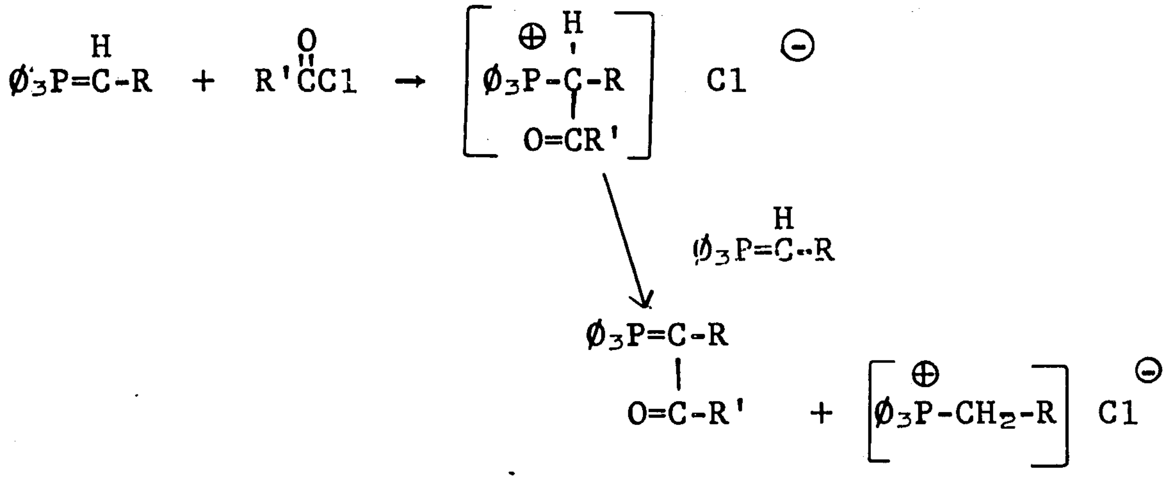


Figure 9

LXXV. (Figure 10). The feasibility of such a synthesis is

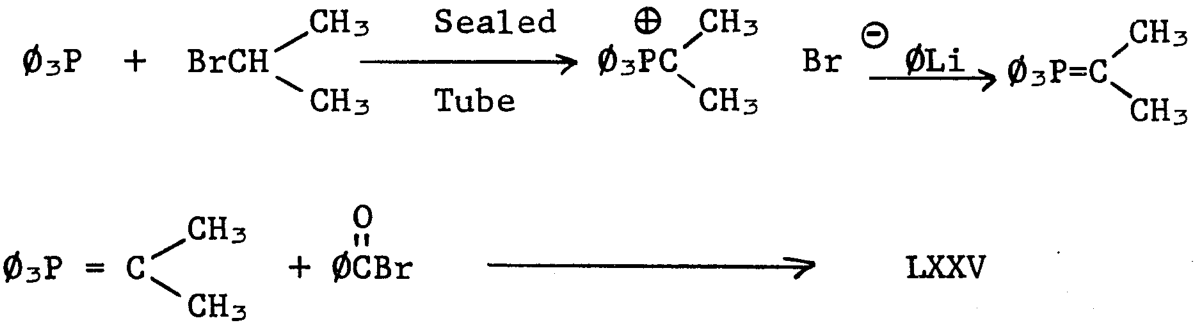
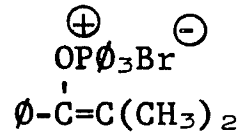


Figure 10

now being investigated in this laboratory.

As indicated in Table VI, α-bromoisobutyrophenone is the only bromoketone studied in the substituted acetophenone series that does not give a C-phosphonium salt in refluxing benzene. The reaction in benzene gives instead mainly isobutyrophenone, which probably arises from the hydrolysis, during workup, of the enol phosphonium salt LXXIX.



$$\phi-\overset{\overset{\oplus\qquad\ominus}{OP\phi_3Br}}{\overset{|}{C}}=C(CH_3)_2$$

LXXIX

Methacrylophenone (LXXVI) may here arise from either direct elimination of hydrogen bromide from the bromoketone or from the elimination of both hydrogen bromide and triphenylphosphine from the undetected α-phosphonium salt LXXV. Seeming support for the hypothesis that elimination of hydrogen bromide caused by triphenylphosphine may occur is the formation of some LXXVI even in methanol (12% yield, in reaction with one equivalent of triphenylphosphine). However, the basicity of triphenylphosphine (pKa=2.73) is low.(39) Only tertiary amines, such as triethylamine (pKa=10.7), are known (36) to dehydrohalogenate α-bromoisobutyrophenone to give LXXVI. Ammonia,(40) methylamine(41), and dimethylamine(42) are reported to give the corresponding α-amino-, α-methylamino-, and α-dimethylaminoisobutyrophenones. However, direct displacement of bromide ion (SN_2) by triphenylphosphine is surely unlikely because of steric hindrance.

The predominant product in benzene, LXXIX, may be formed by one of the two mechanistic pathways already mentioned: either by direct attack on oxygen by the phosphorus or more likely, via initial attack on the halogen by phosphorus. The further interaction of the enolate bromophosphonium ion-pair would be expected to give enol phosphonium salt formation, LXXIX, in this case due to hindrance at the carbanion site of the ambident enolate anion.

The further reaction of the formed methacrylophenone (LXXVI) with triphenylphosphine and hydrogen bromide in benzene was not observed. This may be due to the loss of hydrogen bromide from the refluxing benzene solution. In the actual preparation of the β-phosphonium salt LXXI, hydrogen bromide had to be bubbled in continuously into the mixture of LXXVI and triphenylphosphine at refluxing xylene temperature. Without acid the Michael addition of the phosphine to LXXVI would be reversible in favor of the starting compounds.

As indicated in Table VI, two effects were noted in acetonitrile: (1) the β-phosphonium salt LXXI was now obtained in 48% yield and (2) more elimination products (LXXVI + LXXI), 61% than isobutyrophenone, 29%, were found. One possible explanation for the isolation of more β-phosphonium salt LXXI than isobutyrophenone could be that the direct elimination of hydrogen bromide predominated in acetonitrile over the reaction pathways leading to O-phosphonium salt formation. However, this seems unlikely since elimination is usually better in less polar not more polar media. A more probable explanation appears to be that the polar solvent enhanced the initial formation of the α-phosphonium salt LXXV over the enol phosphonium salt LXXIX. In acetonitrile, the ionic intermediates present are solvated and further apart than in benzene. Because of the greater charge density an oxygen, the enolate ion is primarily solvated on oxygen and therefore there will be less reorganization of solvent molecules in C-phosphorus bond formation. Moreover, if any pentacovalent intermediate is present, its ionization to the final product will also be aided by external solvation.

The α-phosphonium salt LXXV formed decomposes then to LXXVI which reacts in a known manner with hydrogen bromide - triphenylphosphine to give the β -phosphonium salt LXXI. Such a conversion in acetonitrile but not in benzene might possibly be due to the greater solubility and consequently less loss of hydrogen bromide in acetonitrile. As in benzene, however, the enol phosphonium salt hydrolyzes with water from the air during workup to give isobutyrophenone.

The instability of the α-phosphonium salt might be due to steric factors. Thus it is claimed,(34) that t-butyltriphenylphosphonium bromide decomposes to isobutylene, hydrogen bromide and triphenylphosphine on standing. However, the instability of the α-phosphonium salt remains to be tested perhaps by the synthesis already outlined.

α-Bromodeoxybenzoin (desyl bromide) reacted with triphenylphosphine in refluxing benzene to give the expected α-phenylphenacyltriphenylphosphonium bromide LXXII.(Refer to Table VII). In addition to phenyl absorption at 7.0-8.5 δ, the NMR spectrum of LXXII shows a doublet at 8.96 δ , J=12.5 cps, which is assigned, on the basis of deuterium exchange (D_2O), to the single non-aromatic proton. The splitting is undoubtedly due to coupling with P^{31} as evidenced by the large coupling constant. It is perhaps not surprising that the lone aliphatic proton appears downfield from the aromatic protons because strong deshielding by the adjacent moieties would be expected.

LXXII was converted to the corresponding ylide, α-phenylphenacyltriphenylphosphorane (LXXX) in 88% yield when it was stirred briefly at room temperature with an equivalent amount of sodium methoxide in anhydrous methanol. LXXX has also been synthesized by the benzoylation of benzylidenetriphenylphosphorane.(38) Unlike the α-alkylphenacyltriphenylphosphoranes,(26,38) LXXX is stable to hydrolysis.(38) However on pyrolysis at 300° LXXX gives diphenylacetylene.(43)

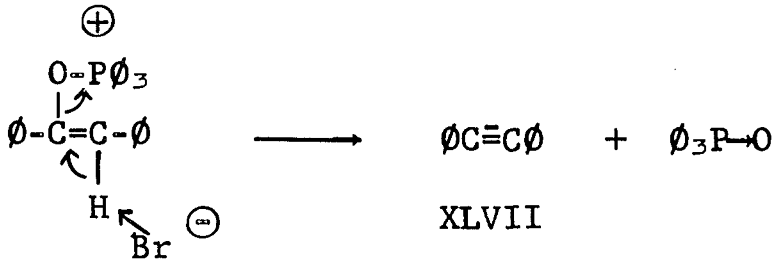
Table VII

Reaction of α-Bromodeoxybenzoin with Triphenylphosphine(a)

Reaction Conditions:	Yields, %				
	$\overset{+}{\text{CP}}$ LXXII	Ylid	$\phi\overset{O}{\overset{\|\|}{C}}CH_2\phi$	$\phi C \equiv C\phi$	ϕ_3PO
In refluxing benzene	58		35(b)	4(d)	43
In refluxing benzene with excess methanol added	-	-	100(c)		100
In benzene with excess diethylmalonate added, 110°	62		31(c)	5(c)	25
In refluxing acetonitrile	3	26(d)	31(c)	39(c,d)	73

(a) All products gave satisfactory analyses or infrared spectra or melting points and were compared to genuine samples by thin layer chromatography. (b) Determined by formation of the 2,4-dinitrophenylhydrazone. (c) Determined by v.p.c. (d) Determined by U.V.

LXXX could not be separated from triphenylphosphine because of their similar solvent properties. However, LXXX was easily detected by IR and on TLC (25% methanol-benzene), LXXX generally gave a spot just above that of triphenylphosphine oxide. As is indicated in Table VII, less C-phosphonium salt LXXII (58%) was obtained in benzene than in the phenacyl bromide and α-bromopropiophenone cases (85%). The reduced yield is probably due to a steric effect of the α-phenyl group. The deoxybenzoin is formed either from the hydrolysis of the enol phosphonium salt LXXXI by moisture from the air or, less likely, in solution. The diphenylacetylene (XLVII) could come only from LXXXI, (cf. LXVI),(16,17,21) since control experiments indicated


LXXXI

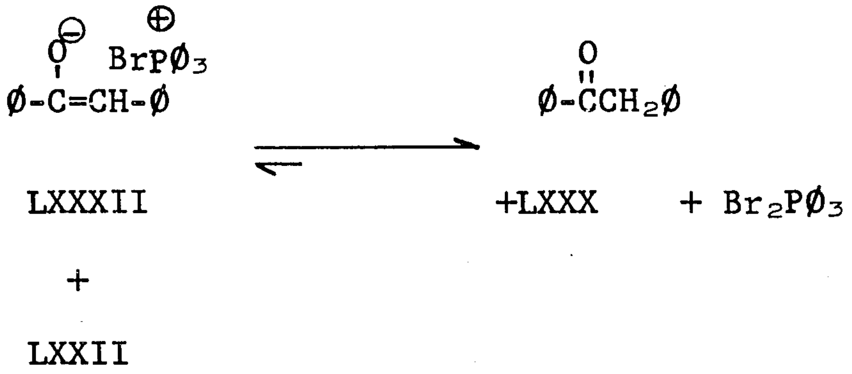
XLVII

that both LXXII and the corresponding ylide LXXX, once formed, are stable at the refluxing temperatures employed.

The finding of a mixture of LXXII, deoxybenzoin and LXVII, is perhaps additional evidence against a postulated rearrangement of enol phosphonium to C-phosphonium salts in this case and the other cases studied. The known enol phosphonium salts, XXXV(17) and XLII(22), once formed, apparently do not rearrange to the C-phosphonium salts.

The reaction in methanol again indicates interception of the enolate formed from initial attack on bromine by triphenylphosphine. The reaction in malonate gave about the same results as in benzene and in each case the C-phosphonium salt LXXII precipitated mainly from solution and hence underwent no further reaction.

There seem to be several possible ways to interpret the results in acetonitrile (refer to Table VII). The C-phosphonium salt LXXII is formed but stays in solution where it can now give a proton to the enolate LXXXII (Figure 11).



$$\underset{\text{LXXXII} + \text{LXXII}}{\phi\text{-}\overset{\overset{\ominus}{O}\ \ \overset{\oplus}{Br}P\phi_3}{C}\text{=CH-}\phi} \rightleftharpoons \phi\text{-}\overset{O}{\overset{\|}{C}}CH_2\phi + \text{LXXX} + Br_2P\phi_3$$

Figure 11

The ylide LXXX and ketone are thus formed. LXXX may also take a proton from desyl bromide to give back LXXII and bromoenolate LXXXIII (Figure 12). LXXXIII as well as LXXXII are both converted to O-phosphonium compounds which can go to diphenylacetylene (XLVII).

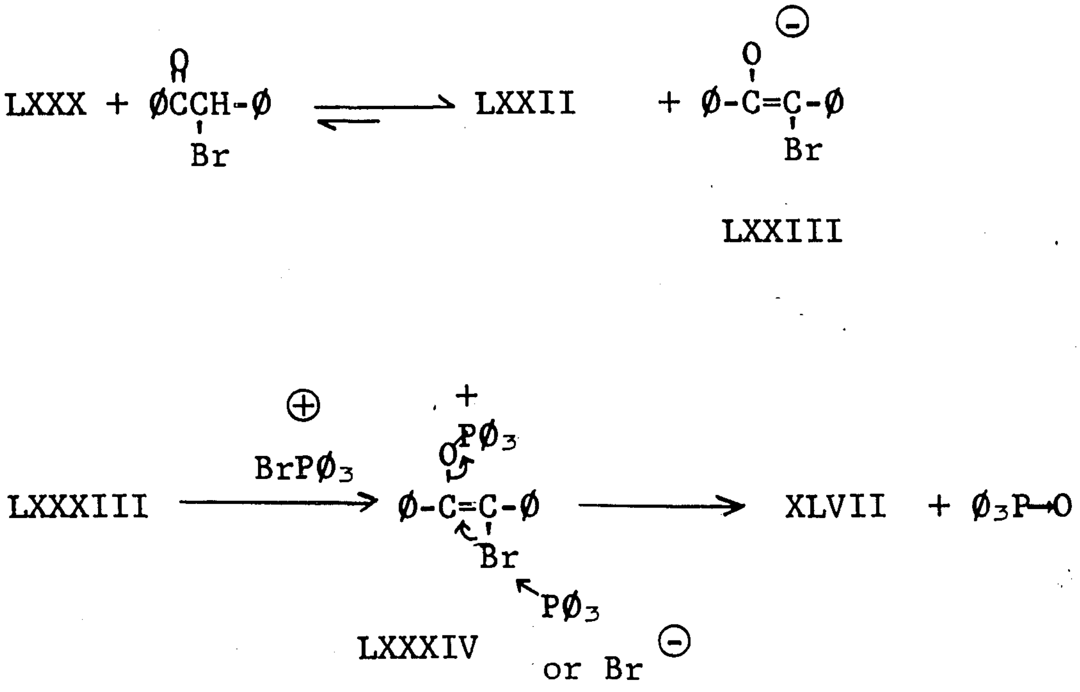
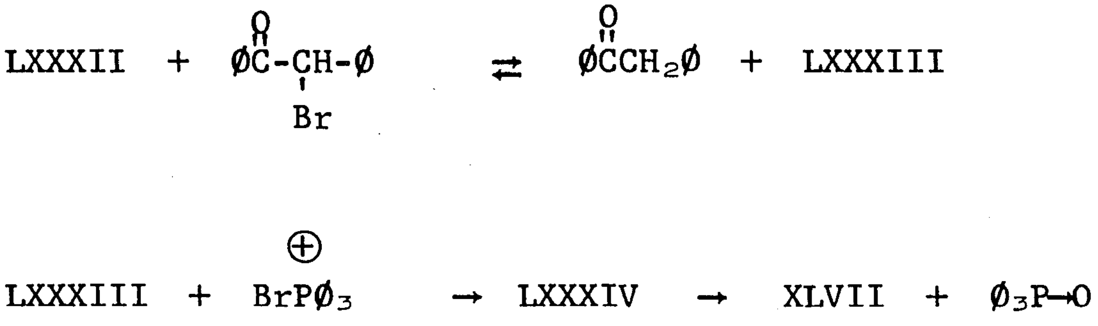


Figure 12

This series of equilibria are suggested to explain the essentially equal yields of deoxybenzoin, diphenylacetylene and the formation of both the C-phosphonium salt LXXII and the ylide LXXX. Only in the desyl halide cases was ylide observed.

Another possibility, which is less likely, is the direct proton exchange between the enolate LXXXII and desyl bromide. (Figure 13).



$$\text{LXXXII} + \phi\overset{O}{\overset{\|}{C}}\text{-}\underset{Br}{CH}\text{-}\phi \rightleftarrows \phi\overset{O}{\overset{\|}{C}}CH_2\phi + \text{LXXXIII}$$

$$\text{LXXXIII} + \overset{\oplus}{BrP\phi_3} \rightarrow \text{LXXXIV} \rightarrow \text{XLVII} + \phi_3P\rightarrow O$$

Figure 13

In some support of the idea that the bromoenolphosphonium salt LXXXIV can give XLVII, perhaps even more readily than does the enol phosphonium salt XLVI, is the finding that α,α-dibromodeoxybenzoin gives XLVII in 49% yield along with desyl bromide (6%) and deoxybenzoin (2%). The discussion of the dihaloketones will follow.

As is indicated in Table VIII, the reaction of desyl chloride (XLV) with triphenylphosphine gives a mixture of C-phosphonium salt (LXXXV and LXXX) and O-phosphonium salt XLVI, with the latter product apparently formed in a greater

Table VIII

Reaction of α-Chlorodeoxybenzoin with Triphenylphosphine(a)

Reaction Conditions:	Yields, %					
	$\overset{+}{\text{CP}}$ LXXXV	Ylid	$Ø\overset{O}{C}CH_2Ø$	$ØC{\equiv}CØ$	$Ø\overset{O}{C}\text{-}\overset{Cl}{C}HØ$	$Ø_3PO$
In refluxing benzene	12	9(c)	31(b)	17(b)	25(b)	82
In refluxing benzene with excess methanol added	-	12(c)	69(b)	2(b)	11(b)	63
In benzene with excess diethylmalonate added, at 110°			40(b)	40(b,c)		78
In refluxing acetonitrile	18-19(d)		39	21(c)	9(f)	75

(a) All products gave satisfactory analyses or infrared spectra or melting points and were compared to genuine samples by thin layer chromatography. (b) Determined by v.p.c. (c) Determined by UV. (d) A mixture of the ylid and phosphonium salt was obtained. (e) All are isolated yields. (f) Determined by halogen analysis.

amount on the basis of the detected yields of its further reaction products-deoxybenzoin and diphenylacetylene (XLVII). It should be remembered that phenacyl chloride and triphenylphosphine give only the C-phosphonium salt LXVIII (SN_2 displacement) and that α-chloro- α,α-diphenylacetophenone gives only the enol phosphonium salt XLII,(22) probably via attack on chlorine (although this has not been shown as yet). Desyl chloride is an intermediate case and a comparison of the series would seem to indicate that the quantity of enolphosphonium salt increases with increasing positive polarization of the halogen and increasing stability of the carbanion remaining.

In refluxing benzene, contrary to the work of Trippett(9) who reported a 90% yield of XLVII, only a 17% yield of XLVII was obtained.(44) The recovery of XLV (25%) would seem to indicate that the reaction is slower than in the desyl bromide case. The higher acetylene/ketone ratio here than in the corresponding bromoketone case (Table VII) could perhaps be due to the fact that the chloride ion is more nucleophilic than the bromide ion and hence acetylene formation from the enolphosphonium salt is facilitated.

In the presence of methanol, the C-phosphonium salt was still formed (12% yield).(Table VIII). Hence it would appear that either part of the C-phosphonium salt LXXXV is formed by direct SN_2 displacement or, less likely that a portion of the enolate intermediate "escapes" interception in methanol. The small yield (2%) of XLVII probably still is formed from enolphosphonium salt XLVI decomposition in competition with its solvolysis to deoxybenzoin. As has already been indicated, the ylide LXXX decomposition to LXVII in solution probably can be eliminated as a possibility.

As can be seen from Table VIII, the product ratios are not that different in benzene, malonate or acetonitrile and are similar to the desyl bromide case in acetonitrile. The main features are the high O-phosphonium (OP^+)/C-phosphonium (CP^+) ratios in all cases with some interception of the C-phosphonium salt LXXXV formation by methanol but not by diethylmalonate. The acetonitrile product ratios here are about the same as in the desyl bromide cases. All of the desyl chloride runs may be explained by exchange reactions similar to those already postulated for the desyl bromide reaction in acetonitrile. In each of these cases the C-phosphonium salt remains in solution. The high OP^+/CP^+ ratio alternatively may be due to more reaction of the enolate intermediate on oxygen rather than on carbon with the more reactive, less stabilized chlorotriphenylphosphonium ion as compared with the more stabilized bromotriphenylphosphonium ion. This possible effect of C-vs O-phosphonium salt formation with chloro- or bromophosphonium ions will be investigated.

In summary, for the desyl chloride case, the products probably arise by a combination of SN_2 displacement (minor pathway) and attack on chlorine (major pathway). Compare with only O-phosphonium salt formation for the α,α-dichlorodeoxybenzoin case (see below). However, the desyl chloride reactions are quite complex and do not lead to as high yields of diphenylacetylene as had been originally expected based on Trippett's work.(9)

Initial studies with α,α-dibromodeoxybenzoin gave reasonable diphenylacetylene yields (49%, in xylene with two equivalents of triphenylphosphine) as well as desyl bromide (6%) and even some deoxybenzoin (2%). In the presence of methanol, monodebromination was observed. In the xylene reaction, it is not known how the remainder of the α,α-dibromodeoxybenzoin is consumed. But an unidentified organophosphorus product was obtained which, however, on the basis of spectral evidence seemed to contain mostly a complex salt of triphenylphosphine.

The reaction of α,α-dichlorodeoxybenzoin with two equivalents of triphenylphosphine in xylene gave the O-phosphonium salt LXXXVI (in 51% yield), and diphenylacetylene (in 31% yield). LXXXVI decomposed on exposure to moisture to desyl chloride and triphenylphosphine oxide. LXXXVI has been characterized by Hoffmann(17), in a brief communication, on the basis of the reactions shown in Figure 14. However, preformed desyl chloride could have equally well been brominated.

The point of interest in these dihaloketone reactions is that here is proof that nucleophilic attack, probably by

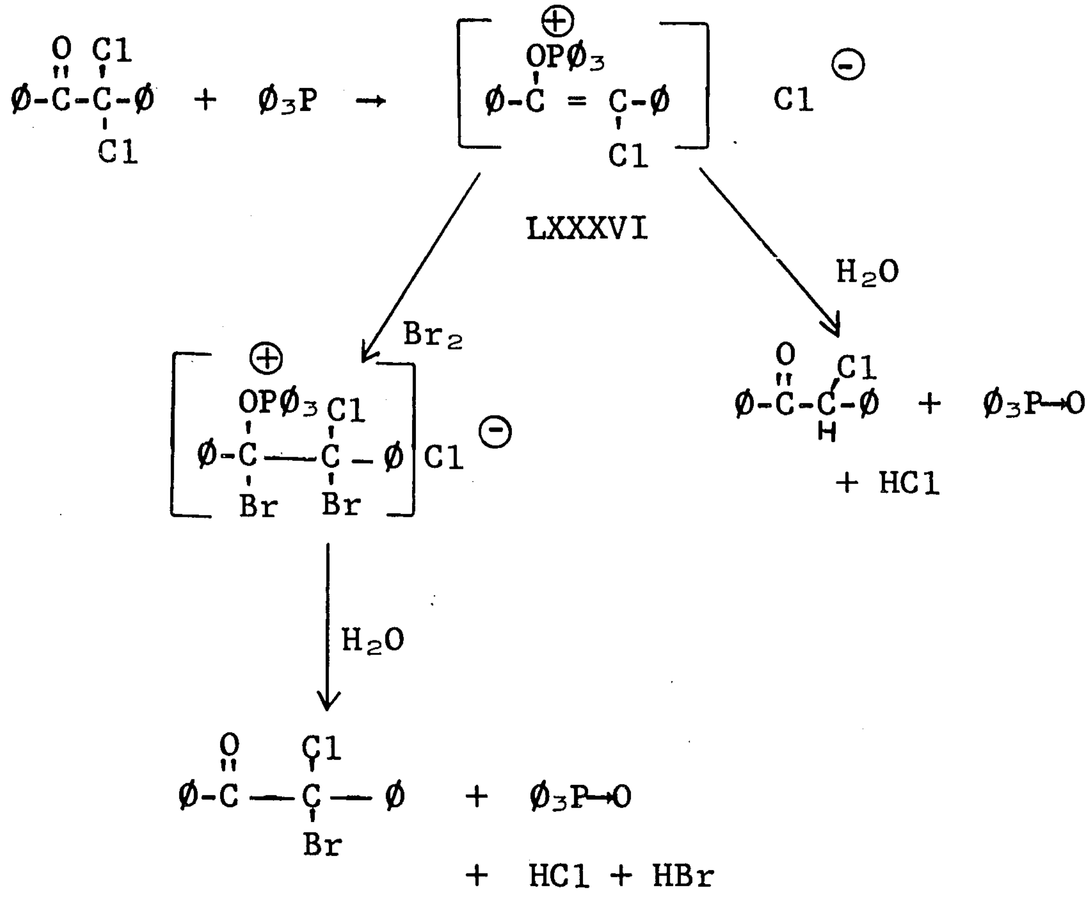
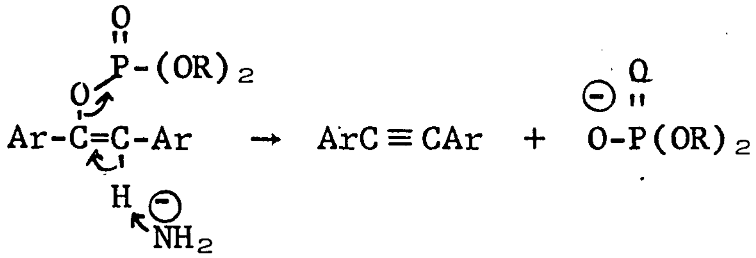


Figure 14

triphenylphosphine, as feasible on this type of vinyl halogen to give acetylene. Therefore, it seems that these reactions and those of the α-haloketones, which proceed probably via the enol phosphonium salts XLVI, LXXXIV, and LXXXVI, may be developed further to give better yields of diphenylacetylene. A comparison with similar reactions of enol phosphates(45) (Figure 15.) should also be undertaken in order to evaluate the relative merits of phosphine oxide and phosphate as leaving roups.



$$\mathrm{Ar{-}C{=}C{-}Ar} \rightarrow \mathrm{ArC{\equiv}CAr} + {}^{\ominus}\mathrm{O{-}P(O)(OR)_2}$$

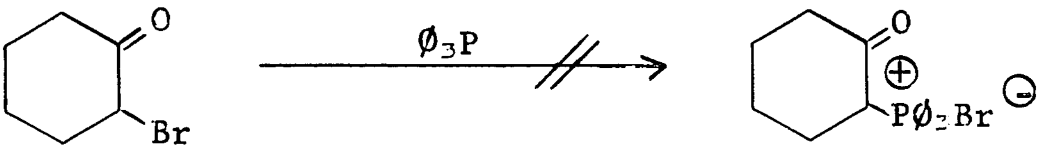
Figure 15

The reactions of α, α-dibromopropiophenone and α,α-dibromoacetophenone with triphenylphosphine were very complex and generally gave unstable phosphorus species from which no pure substances, other than triphenylphosphine and triphenylphosphine oxide, could be isolated. Secondary reactions seemed also to occur during the workup and a variety of hydrolysis products, including the corresponding monohaloketones and dehalogenated ketones, was obtained.

Only traces of methylphenylacetylene, were detected by TLC and by UV when the α,α-dibromopropiophenone reaction was performed in refluxing xylene. When α,α-dibromoacetophenone was heated with triphenylphosphine at 200° without solvent, a yellow liquid was obtained in low yield which gave one spot on TLC. Its NMR spectrum showed a very complex multiplet of about twenty peaks centered at 7.17 δ and a sharp singlet at 6.90 δ. Similar NMR spectra have been reported by Colthrup and co-workers(46) for various trimers of phenylacetylene.

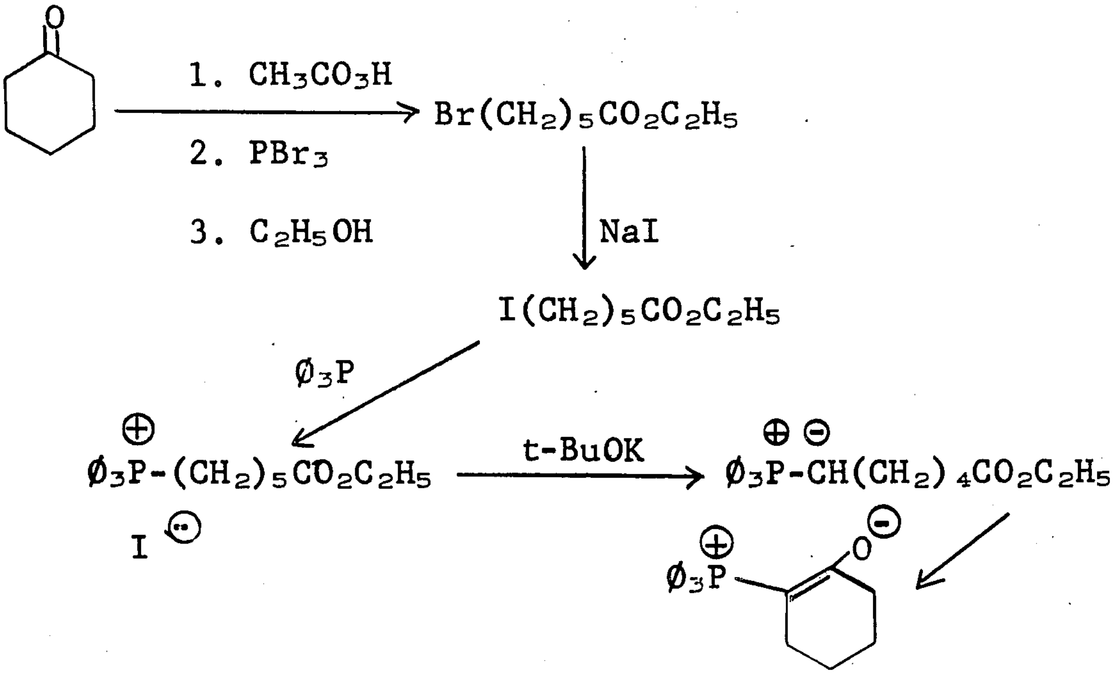
It would appear, therefore, that perhaps the method by which diphenylacetylene was synthesized cannot be simply extended to yield less substituted acetylenes - at least, not with triphenylphosphine.

The reaction of α-bromocyclohexanone(LXXXVII) with triphenylphosphine in the initial presence of methanol is known to lead to the dehalogenated ketone.(16) If LXXXVII is refluxed in benzene for 1.5 hrs. and then ethanol is added to the reaction mixture, cyclohexanone (63%) is still obtained along with ethyl bromide (52%) and triphenylphosphine oxide (95%).(21) However, after long reflux (ca. 24 hrs.) only unidentified resinous oils and dark low-melting phosphorus containing solids are produced. No C-phosphonium salt LXXXIX or α -ketocyclohexylidinetriphenyl-



LXXXVII LXXXIX

phosphorane XC has ever been isolated from the reaction of LXXXVII with triphenylphosphine. However, XC has been synthesized indirectly(47) by the reaction sequence shown in Figure 16.



XC

Figure 16

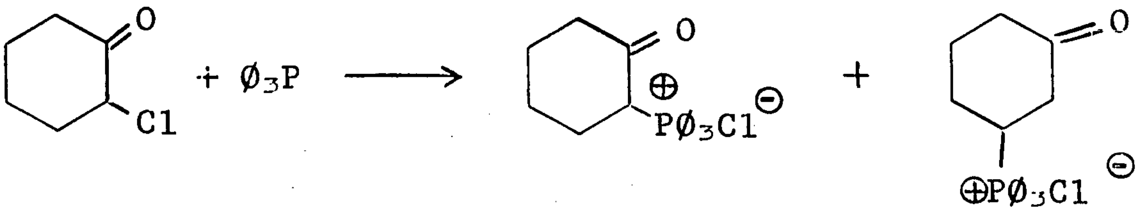
These results suggest that an O-phosphonium salt is formed in the reaction of LXXXVII with triphenylphosphine. Such a salt then probably decomposes to products other than cyclohexanone after long reflux. Hudson's(37) frontier electron density MO calculations predict O-phosphonium salt formation in LXXXVII and C-phosphonium salt formation in the phenacyl bromide case. However, this method does not consider solvent effects, severe steric hindrance nor possible chloro- versus bromophosphonium cation differences.

In an attempt to detect enolate formation, the reaction of LXXXVII with triphenylphosphine was performed in the presence of excess diethylmalonate at room temperature. It was found by v.p.c. that the distilled material contained cyclohexanone (29%) and unreacted LXXXVII (37%). However, the solid distillation residue was a very complex mixture from which no pure substances, other than triphenylphosphine (27%) and triphenylphosphine oxide (19%), could be isolated. When the reaction in diethylmalonate was conducted at 120°, the distillate contained cyclohexanone (24%) and an unidentified material which probably is not 2-cyclohexenone (no UV maximum at 225 mµ). No unreacted LXXXVII was detected . The distillation residue was a very complex mixture whose NMR spectrum ($CDCl_3$) showed only phenyl hydrogens (7.2-8.0 δ) and small signals due to diethylmalonate protons.

The formation of the cyclohexanone might appear to provide some evidence for the enolate mechanism in the LXXXVII case, but since about a 15% yield of cyclohexanone was obtained also in acetonitrile, such a conclusion seems unwarranted. Moreover, it is not clear how the rest of LXXXVII is consumed, as the other products of the reaction are not known.

No reaction of α-chlorocyclohexanone (XCI) with triphenylphosphine was observed even on prolonged refluxing in acetonitrile or in benzene (with two equivalents of triethylamine added). In hexamethylphosphoric triamide at 180° a complex series of color changes was observed, but TLC showed mostly starting materials. Distillation of the high boiling solvent left a purple oil from which, however, no pure substances could be obtained.

Recently, however, Hudson(37) has reported that XCI reacts in boiling dibutyl ether at 140° to give a mixture of the α -and β -ketophosphonium salts, ca. 30% yield (Figure 17).

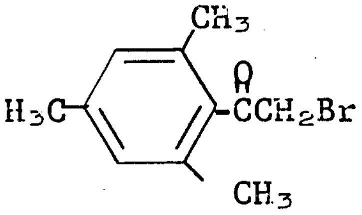


XCI XCII LXXVII

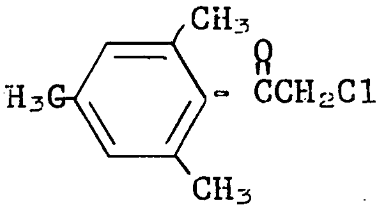
Figure 17

XCII was identified by conversion to the know ylid XC and the structure of LXXVII was confirmed by synthesis from cyclohexenone, triphenylphosphine and hydrogen chloride.

The very large difference in reactivity between the chloro- and bromocyclohexanones suggests that the O- phosphonium salt is not produced by attack on the carbonyl oxygen. Otherwise the reactivity of the chloro compound would be considerably greater since both halogen atoms can be in the axial position which is conducive to facile elimination. The results seem to be more in agreement with the proposed attack on the bromine atom, which is considerably more electrophilic than chlorine, and with a direct S_N2 displacement of the chlorine atom as proposed for phenacyl chloride. In strong support of these ideas Hudson(48) has recently reported that the substituted phenacyl bromide XCIII reacts rapidly (by attack on bromine) with triphenylphosphine to give a mixture of products whereas the corresponding phenacyl chloride XCIV is very inert.



XCIII



XCIV

SUMMARY

In this thesis are reported the results of a preliminary survey of the reactions of a series of alpha-bromoketones with triphenylphosphine. It has been found that generally both C-phosphonium and O-phosphonium salt formation occurs in non-hydroxylic solvents but that only dehalogenation takes place in the presence of methanol. These processes have synthetic value. It is concluded that formation of C- or O-phosphonium salts is most probably not a one-step process. In methanol the most likely process involves initial attack on bromine to give an enolate bromotriphenylphosphonium ion-pair. The ion-pair reacts with methanol to give the dehalogenated ketone, triphenylphosphine oxide and methyl bromide. The latter is trapped to a varying extent with unreacted triphenylphosphine to give methyltriphenylphosphonium bromide.

Reaction in benzene may occur via similar ion-pairs which now interact to give the observed C-phosphonium salts and the non-isolable O-phosphonium salts in varying ratios. Alternate but less likely mechanistic pathways are discussed. Reaction in solvents more polar than benzene gave either

results similar to those obtained in benzene or were characterized by the formation of the products of further reactions.

In contrast to the bromoketone results the reactions of phenacyl chloride and alpha-chloroacetone with triphenylphosphine are not intercepted by methanol and appear to proceed via S_N2 displacement of chloride ion. The reactions of desyl chloride probably still involve some S_N2 displacement but are otherwise similar to those of desyl bromide in the number of products formed.

The reactions of alpha, alpha-dihaloketones give no C-phosphonium salts but yield a mixture of products including monohaloketones and diphenylacetylene. These products are rationalized as all arising from enol phosphonium salts.

The ratio of C- and O-phosphonium salt formation is postulated as being influenced by steric and other factors. The initial site of attack by phosphorus is believed to be dependent upon various factors including the "polarizability" of the halogen.

EXPERIMENTAL

Melting points were determined in Kimax capillary tubes using a "Mel-Temp" apparatus (Laboratory Devices, Box 68, Cambridge, Mass.) and are uncorrected.

The micro-analyses were performed by Dr. V. B. Fish of Lehigh University and by Schwartzkopf Microanalytical Laboratories, Woodside, New York.

Infra-red (IR) spectra were recorded either on a Perkin-Elmer Model 21 or on a Beckman IR-8 spectrophotometer. Ultraviolet (UV) spectra were recorded on a Beckman DK-2A spectrophotometer.

Gas-liquid chromatography (v.p.c.) was carried out on an Aerograph Autoprep A-700 using the columns indicated. Helium was used as the carrier gas.

The nuclear magnetic resonance (NMR) spectra were obtained at 60Mc. on a Varian Model A-60 spectrometer using tetramethylsilane as an internal standard.

Thin layer chromatography (TLC) was performed by the ascending technique on Brinkmann Silica Gel HF_{254}, unless specified otherwise, activated at 110-120°. The thickness of the adsorbent layer was adjusted to 0.25 mm. using "Desaga" equipment supplied by the Brinkmann Co., Inc., Great Neck, Long Island, N.Y. The most frequently used solvent systems were:

Solvent A - 5% (by volume) ethyl acetate in benzene
Solvent B - 5% (by volume) methanol in benzene
Solvent C -15% (by volume) methanol in benzene
Solvent D -25% (by volume) methanol in benzene
Solvent E-1:1 (v./v.) ethyl acetate-methanol

The spots were located with ultraviolet light or were exposed by iodine vapor or 2,4-dinitrophenylhydrazine spray. In addition to comparing the R_f values with those of authentic materials spotted on the same plate, the spots were routinely scraped off the developing plates and were extracted with a suitable solvent (usually 95% ethanol). After removal of the adsorbent by centrifugation, a UV spectrum of each spot was obtained and compared to the UV spectrum of the authentic material.

All reactions between the α-haloketones and triphenylphosphine were carried out in an atmosphere of pre-purified nitrogen (Matheson) with magnetic stirring of the solutions.

Materials:

The triphenylphosphine was obtained from M and T Chemicals, Inc., and was recrystallized either from 95% ethanol or from diethyl ether. After drying at a pressure of 0.1 mm over phosphorus pentoxide, the triphenylphosphine, m.p. 80-81°, was stored in a desiccator over calcium chloride.

α-Chloroacetone was bought from Eastman Organic Chemicals, Rochester, New York, and was distilled from magnesium oxide just before use, b.p.119-119.5°.

Phenacyl chloride and phenacyl bromide were obtained from Matheson Coleman and Bell, East Rutherford, New Jersey, and were recrystallized (charcoal) from 95% ethanol or from n-hexane, m.p.'s 54-56° and 49-50° respectively. α-Chlorodeoxybenzoin, recrystallized from n-hexane, m.p. 66.5-68°, and α-chlorocyclohexanone, redistilled before use, b.p. 90-91°(14-15 mm), were gotten from Aldrich Chemical Co., Milwaukee, Wisc.

α-Bromopropiophenone:

The procedure of Higginbotham, Lapworth and Simpson(49) was used. To propiophenone (Matheson: 134.17 g., 1 mole) dissolved in 200 ml. of anhydrous diethyl ether at room temperature (about 25°) was added bromine (159.83 g., 1 mole) from a Hirschberg funnel during about 90 minutes. After magnetic stirring for an additional hour, the solvent was evaporated at aspirator pressure (14-15 mm) and the residual liquid first distilled through a 7 cm. Vigreux-Claisen distilling head. The fraction boiling at 132-135° (15 mm) was redistilled through a vacuum-jacketed, silvered 22 cm. Vigreux column equipped with a vacuum distilling head. The yield of α -bromopropiophenone was 160.24 g., (75%), b.p. 156-157.5° (42 mm). [B.p.lit.(49) 110-112° (4 mm)] . Caution: lachrymator.

<u>Anal</u>. Calcd. for: C_9H_9BrO:Br 37.50

Found: Br 37.71

<u>α -Bromoisobutyrophenone</u>:

According to the method of Boyer and Straw,(50) isobutyrophenone (Matheson, 29.6 g.,0.2 mole) and bromine (32 g., 0.2 mole), using a few drops of glacial acetic acid to initiate the reaction, yielded 37.86 g., (73%) of almost colorless liquid, b.p. 131-134° (15-16 mm): [b.p. lit.(50) 119-120° (10mm)] . The compound was also obtained from Aldrich, redistilled, b.p. 149-150° (37mm).

α-Bromodeoxybenzoin (Desyl Bromide):

Made by the method of Limpricht and Schwanert,(51) deoxybenzoin (Eastman; 25.0 g., 0.127 mole) and bromine (20.8 g., 0.13 mole) in diethyl ether yielded 29.4 g., (84%) m.p. 54.5-56° (ethanol) [m.p. lit.(51) 54-56°] .

α,α—Dibromoacetophenone:

Acetophenone (Aldrich, 30.0 g., 0.25 mole) and bromine (80.0 g.,0.50 mole) in dry glacial acetic acid, using procedure of Krohnke,(52) gave α,α-dibromoacetophenone, 55.0 g., (80%), m.p. 34-36° (ethanol) [m.p. lit.(52) 35-36°] .

α,α-Dibromopropiophenone:

According to the method of Levine and Stephens,(53) to propiophenone (13.4 g., 0.1 mole), dissolved in chloroform, was added bromine (33.6 g., 0.22 mole) to yield a nearly colorless liquid, 26.3 g., (90%), b.p.180-181° (63 mm), [b.p. lit.(53) 180° (64 mm.)] . Caution: lachrymator.

α,α-Dibromodeoxybenzoin:

Deoxybenzoin (10 g., 0.051 mole) and bromine (17.5 g., 0.11 mole) in carbon disulfide gave, using the procedure of Limpricht and Schwanert,(51) α,α-dibromodeoxybenzoin, white crystals, 12.6 g., (70%), m.p. 110-112° (diethyl ether), [m.p. lit.(51) 110 -112°.] .

α,α-Dichlorodeoxybenzoin:

A mixture of benzil (16 g., 0.076 mole) and phosphorus pentachloride (17 g., 0.082 mole) was heated at 95° for 80 minutes.(54) The yellow crystals obtained from the diethyl ether layer were purified by chromatography on a column, 5 cm. in diameter, using 550 g. of acid washed aluminum oxide (Merck) and eluting with 30-40° petroleum ether. Evaporation of the early fractions gave 1.46 g. α,α,α',α'-tetrachlorobibenzyl m.p. 162-165° [m.p. lit.(55) 163°] and from the middle fractions was obtained the desired α,α-dichlorodeoxybenzoin, wt. 9.06 g. (45%), m.p. 60-61.5° (aqueous ethanol); [m.p. lit.(54) 60-61°]. Further elution of the column with 10% (by volume) methanol in benzene gave

3.32 g. benzil, m.p. and m.m.p. 92-95°.

α-Bromocyclohexanone:

Via the procedure of Allinger and Allinger,(56) to freshly redistilled cyclohexanone (30.0 g., 0.306 mole) mixed with 75 ml. water was added bromine (48.3 g., 0.305 mole) to yield 30.40 g., (56%), of a faintly yellow-green liquid, b.p. 73.5-74.0° (2 mm). [b.p. lit.(56) 83° (6mm)]. α-Bromocyclohexanone was stored at -10° in a brown bottle under nitrogen atmosphere and was distilled before each use.

The other α-haloketones which were synthesized, were also stored in brown bottles under nitrogen atmosphere with the liquids placed in a refrigerator (0°) and the solids kept in a desiccator over calcium chloride. All the solvents used in the reactions of α-haloketones with triphenylphosphine were dried. Benzene and xylene (Baker-reagent grade) were distilled from sodium or were refluxed for 24 hours over "dri-Na" (J.T. Baker Chemical Co., Phillipsburg, New Jersey) and distilled. The acetonitrile ("Baker") was distilled twice from phosphorus pentoxide.

Diethyl ether, 60-70° petroleum ether and other alkanes and cycloalkanes commonly used were stored over "dri-Na." The absolute methanol was dried by distillation from magnesium and iodine(57) and was stored under nitrogen. The diethylmalonate was distilled from calcium hydride and was pure by v.p.c.

Reaction of α-chloroacetone with triphenylphosphine:

A. In benzene - acetonitrile:

To a solution of α-chloroacetone (1.39 g., 15 mmoles) in 65 ml. of acetonitrile and 10 ml. of benzene was added triphenylphosphine (4.15 g., 15.8 mmoles). After refluxing for 22 hrs., the solvents were distilled and benzene was added to the residual semi-solid. The precipitated acetonyltriphenylphosphonium chloride (4.52 g., 12.7 mmoles, 84%) was collected by filtration, m.p. 235-242°dec. [m.p. lit.(58) 237° dec.]. Distillation of the benzene and trituration of the residue with 60-70° petroleum ether gave triphenylphosphine oxide (0.21 g., 0.77 mmoles,5%) identified by I.R. ($CHCl_3$). From the petroleum ether solution on cooling was obtained a white crystalline solid, triphenylphosphine (0.67 g., 11% recovery or 1.72 mmoles, based on amount of α-chloroacetone used), m.p. and m.m.p. 77-79.5°.

B. In Methanol-Acetonitrile:

To a mixture of 65 ml. of acetonitrile and 6 ml. of absolute methanol was added α-chloroacetone (1.39 g., 15 mmoles) and triphenylphosphine (4.15 g., 15.8 mmoles). After refluxing for 48 hours, and distilling the solvents, benzene was added to the white residual solid and the benzene-insoluble acetonyltriphenylphosphonium chloride was collected by filtration (4.59 g., 12.9 mmoles, 86%), m.p. 237-241° dec. [m.p. lit(58) 237° dec.]. Evaporation of the benzene and addition of 60-70° petroleum ether gave crude triphenylphosphine oxide (0.25 g., 0.9 mmoles, 6%) identified by IR ($CHCl_3$).

Distillation of the petroleum ether solution to dryness left triphenylphosphine (0.37 g., 6% recovery or 0.6 mmole, based on amount of α-chloroacetone used), m.p. and m.m.p. 77-79°.

Reaction of Phenacyl Chloride with Triphenylphosphine:

A. In Benzene:

Phenacyl chloride (2.00 g., 12.9 mmoles) and triphenylphosphine (3.41 g., 13.0 mmoles) were refluxed in 35 ml. of benzene for 24 hrs. to give phenacyltriphenylphosphonium chloride (4.35 g., 10.4 mmoles, 80%) as an insoluble powder with m.p. 263-266° dec. [m.p. lit.(58) 254-255°]. The benzene solution by TLC (solvent A) contained only unreacted starting materials. Evaporation to dryness and trituration with 60-70° petroleum ether gave additional phenacyltriphenylphosphonium chloride (0.70 g., 1.68 mmoles, 13%) identified by IR($CHCl_3$). TLC (solvent A) of the petroleum ether solution showed it to contain mostly triphenylphosphine and phenacyl chloride with traces of phenacyltriphenylphosphorane (U.V. λ_{max}^{EtOH} : 267, 274 and 318 mμ (26)) and acetophenone.

B. In Methanol-Benzene:

The same quantities of phenacyl chloride and triphenylphosphine were refluxed in a mixture of 25 ml. of benzene and 10 ml. of methanol for 24 hrs. Distillation of the solvents and addition of benzene gave phenacyltriphenylphosphonium chloride (5.11 g., 12.3mmoles, 95%), m.p. 260-

266° dec. The IR spectrum in chloroform was identical with that of authentic salt. TLC (solvent A) of the benzene solution revealed the presence of unreacted starting materials and, in addition, traces of phenacyltriphenylphosphorane (U.V. λ_{max}^{EtOH} : 267, 273.5, 318mμ (26)).

Reaction of Phenacyl Bromide with Triphenylphosphine:

A. In Benzene:

A mixture of phenacyl bromide (0.744 g., 3.74 mmoles) and triphenylphosphine (1.00 g., 3.81 mmoles) was refluxed in 55 ml. benzene for 1.5 hrs. The resultant precipitate was dried overnight in a vacuum desiccator over calcium chloride to yield phenacyltriphenylphosphonium bromide (1.36 g., 2.95 mmoles), 80%), m.p. 260-264° [m.p. lit.(26) 269-271° after recrystallization from water]. Evaporation of the solvent left a semi-solid to which was added 60-70° petroleum ether to give triphenylphosphine oxide (0.20 g.,0.72 mmole, 19%), identified by melting point and IR spectrum. Distillation of the solvent from the remaining filtrate and addition of 4 ml. of 0.25 M 2,4-dinitrophenylhydrazine solution gave the 2,4-dinitrophenylhydrazone of acetophenone (0.064 g., 0.21mmole, 6%), which was recrystallized from acetic acid; m.p. and m.p. 240-243.5° (m.p. ref. 245-247°).

B. <u>In Benzene-Excess Methanol</u>:

A mixture of phenacyl bromide (1.44 g., 7.22 mmoles) and triphenylphosphine (2.00 g., 7.62 mmoles) was refluxed in 65 ml. of benzene and 8 ml. of methanol for 1.75 hrs. to yield the phosphonium bromide (0.30 g., 0.65 mmole, 9%), identified by melting point and IR spectrum. Triphenylphosphine oxide (1.85 g., 6.56 mmoles, 92%), m.p. and m.m.p. 152-155°, and the 2,4-dinitrophenylhydrazone of acetophenone (0.97 g., 3.23 mmoles, 50%), m.p. 241-245°, were obtained as described in A.

The yield of acetophenone was later checked in this laboratory by v.p.c. and found to be $>$ 88%.(59)

When the same quantities of phenacyl bromide and triphenylphosphine were refluxed in 65 ml. benzene and only 0.40 ml. or 1.45 equivalents of methanol, the products were phenacyltriphenylphosphonium bromide (0.411 g., 0.9 mmole, 12%);

acetophenone-2,4-DNPH (1.80 g., 6.0 mmoles, 86%) and triphenylphosphine oxide (1.152 g., 4.14 mmoles, 54%).

C. <u>In Acetonitrile - Excess Dimedone (5,5-Dimethylcyclohexane-1,3-dione)</u>:

To a solution of triphenylphosphine (2.643 g., 10.05 mmoles) and dimedone (5.601 g., 40 mmoles) in 60 ml. of acetonitrile at 70° was added, during 2 min., a solution of phenacyl bromide (2.002 g., 10.05 mmoles) in 5 ml. of acetonitrile. After heating at an oil bath temperature of 70-75° for 5 hours an insoluble material (6.64 g.) was removed and extracted in a Soxhlet apparatus with 150 ml. benzene for 7 hrs. Benzene-insoluble white crystals, left in Soxhlet cup, were identified as phenacyltriphenylphosphonium bromide (2.40 g., 5.2 mmoles, 52%); m.p. 273.5-275° d. Evaporation of the benzene extracts left dimedone, light yellow needles, (3.94 g., 28.1 mmoles, 70% recovery), m.p. 144-148°; I.R. spectrum ($CHCl_3$) identical with that of starting material.

The original acetonitrile solution was concentrated to a small volume by fractional distillation at atmospheric pressure. To the residual liquid was added 60-80° petroleum ether and an insoluble white solid (2.17 g.) was collected. IR spectrum ($CHCl_3$) indicated that the material was a mixture of dimedone and the phosphonium salt. Extracted with 100 ml. boiling benzene (1/2 hr.) and benzene-insoluble white solid (0.70g., 1.52 mmoles, 15%; m.p. 276-278° dec; total yield: 67%) was collected and identified by IR ($CHCl_3$) as more of the phosphonium salt. Evaporation of the benzene gave more dimedone (1.24 g., 8.86 mmoles, 22%). To the oily petroleum ether solution was added chloroform and the resultant clear yellow liquid was distilled at 75-78° (11mm.) to yield a colorless distillate (0.79 g.) containing acetophenone and 5,5-dimethyl-3-bromocyclohexenone. The two components were detected by TLC (solvent A) and were identified from IR and NMR spectra. (The authentic bromoeneone spectra were obtained from Dr. I. J. Borowitz). NMR (neat) gave signals at: 7.8-8.0 δ (multiplet, <u>ortho</u> H's of phenyl of acetophenone), 7.2-7.5 (multiplet, aromatic H's), 6.3-6.4 (triplet, olefinic H of bromoeneone), 2.58 and 2.55 (doublet), 2.48 (singlet, CH_3-of acetophenone), 2.13 (singlet), and 0.97 δ (singlet, CH_3's - of bromoeneone). A small unidentified singlet was observed at 7.67 δ . Integration of the CH_3-group areas showed the two components to be present in the ratio of 52:48, acetophenone: bromoeneone. Yields: acetophenone (0.41 g., 3.39 mmoles, 34%); bromoeneone, 0.38 g., 1.87 mmoles (19% yield, based on phenacyl bromide as the bromine source).

The distillation residue, a yellow oil, 0.75 g., solidified and its IR spectrum ($CHCl_3$) showed it to be a mixture of dimedone and triphenylphosphine oxide.

D. <u>In Diethylmalonate</u>:

(a) Triphenylphosphine (1.025 g., 3.88mmoles) was added to anhydrous diethylmalonate (30 ml., 31.65 g. or 0.198 mole) and the mixture was stirred for several minutes to achieve homogeneity. Phenacyl bromide (0.776 g., 3.87 mmoles) was added producing a yellow-green color which very rapidly (less than 20 sec.) intensified, and disappeared the moment that white solid appeared throughout the solution. The mixture was then heated at 123° (oil bath) for 6.5 hrs.

During this time the colorless reaction mixture became brown. The solid was filtered and dried for three days in vacuo over calcium chloride. It was identified as phenacyltriphenylphosphonium bromide (1.096 g., 2.38 mmoles, 62%), m.p. 274-278° dec., m.m.p. 274-278° dec. [m.p. ref. 275-278° dec.]. The malonate solution was distilled at 91-95° (20 mm.) and the colorless distillate (30.83 g.) was collected in a receiver cooled with dry ice-acetone. This liquid, based on the amount of salt obtained, should contain about 1.43 mmoles (0.17 g. or ca. 0.6% of the solution of acetophenone.

When a 6' x 1/4" v.p.c. column (20% Carbowax 20 M on 60/80 HMDS, Chromasorb P, column temperature 142°, injector temperature 157°, flow rate 100 ml./min.) was flooded with 24 µl of diethylmalonate solution, a small symmetrical peak for acetophenone was obtained. Comparison of its area to a calibration curve indicated that it represented less than 1% of the total weight of material injected.

The black distillation residue was extracted with benzene, filtered, and the benzene evaporated. The residue 0.21 g., of yellow semi-solid, was by IR($CHCl_3$) triphenylphosphine oxide (0.76 mmole, 19%).

(b) At 25°:

To a solution of triphenylphosphine (1.322 g., 5.04 mmoles) in 15 ml. of anhydrous diethylmalonate (15.82 g., 0.099 mole) was added dropwise during 5.5 hrs. a solution of phenacyl bromide (1.001 g., 5.03 mmoles) in 15 ml. of dry diethylmalonate. The clear colorless solution became milky after 12 min. of addition as a white solid formed. Stirred additional 0.5 hr. the white insoluble solid was collected and dried in vacuo overnight over calcium chloride. Yield of phenacyltriphenylphosphonium bromide (1.854 g., 4.03 mmoles, 80%), m.p. 270-273.5° dec., m.m.p. 270-274° dec. The malonate solution was colorless.

Control Experiments: (a) Stability of Triphenylphosphine in Diethylmalonate:

Triphenylphosphine (0.499 g., 1.9 mmoles) was dissolved in 10 ml. of anhydrous diethylmalonate. The light yellow solution was heated at 125° (oil bath) for 25.5 hrs. No change in color. TLC (solvent A) indicated that the triphenylphosphine was unchanged.

(b) Stability of Phenacyl Bromide in Diethylmalonate:

Phenacyl bromide (0.503 g., 2.5 mmoles) was heated at 127° (oil bath) in 10 ml. of anhydrous diethylmalonate for 24 hrs. TLC (Solvent A) indicated that no reaction had occurred and only phenacyl bromide was present. Solution remained light yellow.

(c) Stability of Phenacyltriphenylphosphonium bromide in Diethylmalonate:

(1) In 10 ml. of anhydrous diethylmalonate was suspended 0.928 g. (2.02 mmoles) of the phosphonium bromide, m.p. 275-278° dec. Heated at 115-120° for 21 hrs. with rapid stirring of the heterogeneous mixture. After cooling, the white insoluble powder was collected and dried in vacuo for several days over calcium chloride to yield 0.830 g. of the phosphonium bromide, m.p. 271-275° dec. Addition of diethyl ether to the light yellow malonate solution precipitated 0.052 g. of white powder which was identified by m.p. and IR ($CHCl_3$) as more of the phosphonium bromide. The total recovery was 0.882 g. (95%).

E. In Ethylcyanoacetate-Benzene:

Triphenylphosphine (5.50 g., 0.021 mole) was dissolved in 40 ml. of benzene. Ethylcyanoacetate (10 ml., 10.63 g., 0.094 mole) was added followed by phenacylbromide (4.00 g., 0.0209 mole). A very rapid reaction ensued and a lot of white solid formed. The mixture was stirred for 2 hrs. at 25° and then heated for an additional 0.5 hr. at 90°. The insoluble white solid was collected and dried in vacuo overnight over calcium chloride (9.10 g., 19.8 mmoles, 95%), m.p. and m.m.p. with phenacyltriphenylphosphonium bromide 269.5-272°. Identified also by UV(EtOH) and by TLC (solvent E). The residual yellow solution on TLC (solvent A) gave spots for triphenylphosphine, acetophenone (UVλ_{max}^{EtOH}: ca. 241 mμ) and triphenylphosphine oxide.

F. In Ethylcyanoacetate - Acetonitrile:

Triphenylphosphine (2.78 g., 0.0106 mole) was added to a solution of acetonitrile (10 ml.) - ethylcyanoacetate (8.64 g., 0.0765 mole). Stirred for several minutes at 35° to achieve homogeneity. Phenacyl bromide (2.00 g., 0.0105 mole) was added, producing an intense yellow green color as a prelude to the very rapid appearance of a white solid. The mixture was stirred for 1.75 hrs. at 25°. Insoluble phenacyltriphenylphosphonium bromide (4.21 g., 9.13 mmoles, 88%), was collected, m.p. 273-276.5° (inserted at 250°); IR spectrum identical with authentic salt. The residual solution gave on TLC (solvent A) spots for triphenylphosphine and acetophenone.

G. In Malononitrile:

A mixture of phenacyl bromide (3.10 g., 15 mmoles) and triphenylphosphine (4.00 g., 15.2 mmoles) was heated at 95° in malononitrile (20 g., 0.303 mole) for 22 hrs. The black-brown solution was distilled to dryness at reduced pressure (15 mm.) and the colorless distillate, 16.49 g., solidified in the receiver. No acetophenone was detected in the distillate by v.p.c. The distillation residue, a tan solid, was placed in a Soxhlet apparatus and was extracted overnight with benzene. The insoluble material, left in the Soxhlet cup, was identified as phenacyltriphenylphosphonium bromide (5.84 g., 12.7 mmoles, 82%), m.p. 264-270°. Evaporation of the benzene extracts left a black tar.

H. In Acetonitrile with Addition of Butyl Iodide:

To a solution of phenacyl bromide (3.10 g., 15 mmoles) and triphenylphosphine (6.50 g., 24.8 mmoles) in 85 ml. of acetonitrile was added n-butyl iodide (8.26 g., 5.1 ml., 46.7 mmoles). The combined mixture was refluxed for 4.5 hrs. The insoluble white solid, 5.29 g., m.p. 250-254°, was collected and identified by TLC (solvent D) as a mixture of phenacyltriphenylphosphonium halides. After removal of the solvent, the residual material was extracted with boiling cyclohexane to give triphenylphosphine oxide (0.42 g., 1.5 mmoles, 10%). The cyclohexane insoluble powder, 3.05 g., was identified by TLC (solvent D) as a complex mixture of n-butyltriphenylphosphonium-and phenacyltriphenylphosphonium halides.

Reaction of α-Bromopropiophenone with Triphenylphosphine:

A. In Benzene:

(a) A mixture of α-bromopropiophenone (6.00 g., 0.0281 mole) and triphenylphosphine (7.42 g., 0.0283 mole) was dissolved in 60 ml. of benzene. The solution remained clear for several minutes, after which a white solid formed. After refluxing for 1.5 hrs., the insoluble white powder was collected and identified as α-methylphenacyltriphenylphosphonium bromide (3.26 g., 6.87 mmoles, 24%), m.p. 239-242° dec. The analytical sample was recrystallized once from aqueous ethanol and melted at 245-247° (m.p. lit.(60) 245-245.5°).

Anal. Calcd. for $C_{27}H_{24}BrOP$: C,68.22; H,5.09; P,6.50

Found: C,68.31; H,5.04; P, 6.66.

IR(KBr): 6.0(s), 6.31(m), 6.73 (m), 6.96(s), 8.24(s), 9.03(s), 10.02(m),10.43(m-s)μ.

NMR($CDCl_3$): A quartet of signals consisting of two doublets centered at 2.04 δ (J=7.5 cps) and 1.73 δ (J=7.5 cps) respectively, (J=19 cps for the coupling between the adjacent doublets) [relative area 2.6 $-CH_3$ group] ; a small multiplet at 8.50-8.81 δ (<u>ortho</u> phenyl H's) and a large complex multiplet at 7.17-8.34 δ (aromatic H's) [relative area of combined multiplets = 20.0] . Because of the low solubility of the phosphonium salt in $CDCl_3$, the complex $\equiv$CH signal was lost in the "noise."

From the residual benzene solid precipitated a white solid which fumed strongly when exposed to air and turned rapidly to an oily sludge. TLC (solvent A) of this material gave a large spot for triphenylphosphine oxide and a faint spot for triphenylphosphine. Ten ml. of methanol was added and the combined solvents were distilled by fractional distillation at reduced pressure. Theresidue by TLC (solvent A) gave spots for the starting materials and for propiophenone and triphenylphosphine oxide. Trituration with 60-70° petroleum ether gave triphenylphosphine oxide (5.10 ., 18.3 mmoles, 65%) identified by TLC (solvent A). Fractional distillation ot the residual solution left an orange liquid wt. 4.43 g., which by TLC (solvent A) contained only triphenylphosphine oxide, α -bromopropiophenone and propiophenone. The mixture was analyzed by quantitative TLC. Found: 2.15 g., (16 mmoles) propiophenone (52%) and 1.05 g. (4.93 mmoles) α - bromopropiophenone (18%). By difference, weight of triphenylphosphine oxide is 1.23 g., 4.47 mmoles, 15%.

Description of quantitative TLC method:

Plates, 20 x 20 cm., coated with a 0.5 mm. layer of Silica Gel HF_{254} were used and the developing solvent was 5% ethyl acetate in benzene. Solutions of known concentrations (1-2 x 10^{-1}M) were prepared for propiophenone and α-bromopropiophenone. Five µl of each solution was spotted on a plate (one spot per plate) with a 5λ pipette. After the solvent front had ascended 15 cm. the spot was located by UV light and the zone of adsorbent was quickly scraped with a razor blade into a centrifuge tube.

Extracted with 95% ethanol, the adsorbent removed by centrifugation and the volume of the solution made up to 10 ml. A UV spectrum of the solution was then taken and the absorbance value at the λ_{max} of the ketone was observed. A blank for each spot was obtained by scraping an adjacent zones of equal area on the same plate and performing all the operations described. The absorbance of the blank solution at the λ_{max} of the ketone was subtracted and the corrected absorbance values were plotted against the number of milligrams of the ketone spotted on the plate.

The unknowns were treated in a similar fashion and the corrected absorbance value for each ketonic component was then compared to the appropriate calibration curve to give the weight of ketone in the solution.

(b) Summary of the runs in which the same quantities of α-bromopropiophenone (6.00 g., 0.0281 mole) and triphenylphosphine (7.42 g., 0.0283 mole) were refluxed in 50-55 ml. benzene for longer periods of time. Yields determined as before.

	% Yields			
Reflux Time (Hrs.)	$C_6H_5\overset{O}{\overset{\|}{C}}-\overset{H}{C}-\overset{\oplus}{P}\phi_3Br^{\ominus}$	$C_6H_5\overset{O}{\overset{\|}{C}}CH_2CH_3$	$C_6H_5\overset{O}{\overset{\|}{C}}-\overset{Br}{C}HCH_3$	$(C_6H_5)_3P\rightarrow O$
10	62	—	—	—
17	73	—	—	—
21	78	19	9	ca.27
31	83	13	9	ca.22

(c) The maximum yield of phosphonium salt was also obtained in the following reaction:

α-Bromopropiophenone (6.00 g., 0.0281 mole) and triphenylphosphine (7.42 g., 0.0283 mole) were refluxed in 32ml.

of benzene for 2 hrs. The insoluble phosphonium salt (5.05 g., 10.6 mmoles, 39%), m.p. 241-245°, was collected under nitrogen. The residual clear solution was fractionally distilled from oven-dried (110°) apparatus and protected from moisture by a phosphorus pentoxide tube. A hard bright white cake of solid remained in distillation flask. Trituration with benzene gave a white powder (6.00 g., 12.7 mmoles, 44%), m.p. 225-239° which was identified by IR ($CHCl_3$) as α-methylphenacyltriphenylphosphonium bromide. Total yield is: 11.05 g., 23.3 mmoles, 83%).

B. In Benzene-Methanol:

A mixture of α-bromopropiophenone (3.00 g., 0.0140 mole) and triphenylphosphine (3.71 g., 0.0142 mole) was refluxed in benzene (23 ml.)-methanol (5 ml.) for 30 hrs. The insoluble white powder, methyltriphenylphosphonium bromide, was collected, (1.66 g., 4.66 mmoles, 33%), m.p. 225-230° and identified by TLC (solvent E) and by IR($CHCl_3$). The yellow reaction solution contained only α-bromopropiophenone, propiophenone and triphenylphosphine oxide (TLC: solvent A). V.p.c. of the solution on a 5 x 1/4" glass column (20%ØF-1 on 60/80 mesh DMCS acid-washed chromasorb G, column temperature 148°, flow rate 66 ml./min.) gave the following results: propiophenone (1.31 g., 9.8 mmoles, ca. 100% yield based on available triphenylphosphine or 70% actual yield) and α-bromopropiophenone (0.98 g., 4.5 mmoles, 32% recovered).

The solvents were then evaporated and n-hexane added. The insoluble white granular solid, was collected and dried overnight *in vacuo* over calcium chloride to yield triphenylphosphine oxide (2.45 g., 8.82mmoles, 93% yield based on available triphenylphosphine or 60% actual yield).

C. In Benzene-Diethylmalonate:

To a solution of triphenylphosphine (3.71 g., 0.0142 mole) in benzene (16 ml.) - diethylmalonate (10 ml., 0.066 mole) -pure by v.p.c. (20% Carbowax) was added a solution of α-bromopropiophenone (3.00 g., 0.0140 mole) in 6 ml. of benzene. The mixture was heated at 85° (oil bath) for 30 hrs. The resulting precipitate of α-methylphenacyltriphenylphosphonium bromide, a brown powder, was collected and washed well with benzene (4.45g., 9.37 mmoles, 67%), m.p.

233-240° dec. IR spectrum ($CHCl_3$) identical with spectrum of analytically pure salt obtained from reflux in benzene alone. The dark-brown solution was distilled through a 7 cm. Vigreux-Claisen distilling head and the fraction with b.p. 45-47 (0.4 mm.) was collected as a colorless liquid and analyzed by v.p.c. (6' column of 20% Carbowax 20M on 60/80 mesh HMDS Chromasorb P, column temperature 142°, flow rate 100 ml./min.). It was found that 4% of the liquid or 0.44 g. is propiophenone (3.28 moles, 23%). The distillation residue was a black tar.

D. In Acetonitrile:

A mixture of α-bromopropiophenone (6.00 g., 0.0281 mole) and triphenylphosphine (7.42 g., 0.0283 mole) was refluxed in 70 ml. of acetonitrile for 31 hrs. The precipitated α-methylphenacyltriphenylphosphonium bromide (8.58 g.) was collected, m.p. 241.5-246.5°. Identified by IR and mixed melting point. Distillation of the solvent and addition of benzene to the oily residue furnished more phosphonium salt (2.22 g.), m.p. 235-241° (identified by IR), total yield:

10.8 g., 22.8 mmoles, 81%). TLC (solvent A) of the benzene solution gave spots for α-bromopropiophenone, propiophenone and triphenylphosphine oxide. After reduction in volume, the benzene solution was chromatographed on a column (2-cm. in diameter) of neutral aluminum oxide (60 g., Brinkmann). Eluted with benzene (300 ml.) and most of solvent distilled at atmospheric pressure. The residual solution was transferred with the aid of methylene chloride to a 10 ml. pear-shaped flask and the rest of the solvent distilled at reduced pressure (13 mm.) through a 7 cm. Vigreux distilling column and head. The yellow liquid, 0.60 g., which remained was placed neat in an NMR tube for analysis. The spectrum showed it to be mostly propiophenone. Signals were obtained at 1.0-1.3 δ (triplet, CH_3-) and 2.6-3.0 δ (quartet, CH_2-). Weak signals for α-bromopropiophenone were at 1.75-1.9 δ (doublet, CH_3-) and 5.1-5.5 δ (quartet $CH\textless$). In addition two complex multiplets were seen at 7.7-8.0 δ (ortho H's of phenyl group) and 7.2-7.5 δ (aromatic H's). The integrated areas, using the CH_3-group signals, gave a ratio of 88:12 for propiophenone to α-bromopropiophenone. Yields: propiophenone (0.53 g., 3.96 mmoles, 14%), α-bromopropiophenone

(0.07 g., 0.33 mmole,ca. 1%).

Elution of the alumina column with 95% ethanol (125 ml.) and evaporation of the solvent gave triphenylphosphine oxide (1.62 g., 5.82mmoles, 20%), identified by IR spectrum ($CHCl_3$).

Potentiometric Titrations of Bromide Ion from the Reaction of α-Bromopiophenone with Triphenylphosphine:

A. A mixture of α-bromopropiophenone (2.9982 g., 14.07 mmoles) and triphenylphosphine (3.71 g., 14.15 mmoles) was refluxed in a 3-neck flask for 2 hrs. in 20 ml. of benzene. Through a rubber septum attached to one of the necks was injected 20 ml. of distilled water. The insoluble α-methylphenacyltriphenylphosphonium bromide was collected and dried overnight in vacuo over P_2O_5, wt. 1.94 g., 29%; 4.08 milliequivalents bromine. The layers were separated and the water layer diluted to 50 ml. and the benzene layer to 100 ml. A 5 ml. aliquot of the water layer was titrated with 0.0500 N silver nitrate solution and the end point was determined potentiometrically. A total of 7.15 ml. of the silver nitrate solution was needed, which indicated that the aliquot contains 0.3575 milliequivalents of bromine. The whole water layer, (X20), therefore, has 3.58 milliequivalents of bromine.

A 5 ml. aliquot of the benzene layer was refluxed for 16 hrs. with 25 ml. of 20% aqueous sodium hydroxide solution. After cooling, the solution was acidified with 1:1 nitric acid a few drops past the phenolpthalein end point or until E (millivolts) of the heterogeneous mixture was greater than 300. A total of 5.65 ml. of 0.0500 N silver nitrate solution was needed to reach the end point. This corresponds to 0.2825 milliequivalents of bromine/5 ml. or 5.65 milliequivalents bromine in the entire benzene layer.

Total bromine accounted for: 13.31 milliequivalents or 94%.

B. A mixture of α-bromopropiophenone (3.0110 g., 14.13 mmoles) and triphenylphosphine (3.71 g., 14.15 mmoles) was refluxed in 17 ml. of benzene for 10 hrs. As before, 20 ml. distilled water was injected. The insoluble phosphonium salt (4.60 g., 9.69 mmoles, 69.5%) was collected and dried overnight <u>in vacuo</u> over phosphorus pentoxide. The liquid layers could only be partially separated due to formation of a persistent emulsion. Sodium nitrate was added and after standing overnight, the emulsion had disappeared and the layers were separated . The water layer was diluted to a volume of 250 ml., the benzene layer to 100 ml. A 25 ml. aliquot of the water layer was further acidified with 3 drops of 1:1 nitric acid. A total of 1.96 ml. of 0.0500 N silver nitrate solution was needed to reach the end point. This corresponds to 0.098 milliequivalents bromine/25 ml. or 0.98 milliequivalents bromine in the whole water layer. A similar titration of a 50 ml. aliquot of the water layer gave a value of 0.99 milliequivalents of bromine in the water layer.

A 5 ml. aliquot of the benzene layer was refluxed with 25 ml. 20% aqueous sodium hydroxide for 12 hrs. Acidified as above. A total of 2.75 ml. of 0.0500 N silver nitrate solution needed to reach end point. Therefore, 0.137 milliequivalents bromine/5 ml. or 2.75 milliequivalents bromine in entire benzene layer.

Total bromine found: 13.42 milliequivalents or 95%.

Control Experiment:

α-Bromopropiophenone (1.9120 g., 8.972 mmoles) was refluxed in 20 ml. of benzene for 2 hrs. after which 20 ml. of 0.16M aqueous nitric acid was injected through the septum. The layers were separated and the benzene layer made up to a volume of 50 ml. The entire water layer was titrated and the end point was reached after 0.125 ml. of 0.0500 N silver nitrate solution had been added. Therefore, 0.006 milliequivalents ionic bromine in water layer.

A 1 ml. aliquot of the benzene layer was refluxed for 11 hrs. with 25 ml. of 20% aqueous sodium hydroxide. Acidified with 1:1 HNO_3 to phenolpthalein endpoint. A total of 3.50 ml. of 0.0500 N silver nitrate needed to reach endpoint. This corresponds to 0.175 milliequivalents bromine/1 ml. or 8.75 milliequivalents bromine in entire benzene layer. Total bromine accounted for: 8.75 milliequivalents, 98%.

Stability of α-Methylphenacyltriphenylphosphonium bromide to Refluxing Methanol:

In 10 ml. absolute methanol was dissolved 0.20 g. of the phosphonium bromide and the solution was refluxed for 30 hrs. TLC (solvent E) indicated that no decomposition of the salt had occurred. After distillation of the alcohol, trituration of the oily residue with 20 ml. of diethyl ether gave an off-white powder which after drying overnight *in vacuo* over calcium chloride weighed 0.196 g., m.p. and m.m.p. 240-243°.

Reaction of α-Bromoisobutyrophenone with triphenylphosphine:

A. In Benzene:

α-Bromoisobutyrophenone (4.00 g., 0.0176 mole) and triphenylphosphine (4.69 g., 17.9 mmoles) were refluxed in 45 ml. of benzene for 24 hrs. A benzene-insoluble white powder, 0.16 g., was collected under nitrogen atmosphere. This material was identified as hydroxytriphenylphosphonium bromide by its IR spectrum (ethanol-free dry chloroform): 3.37(m), 6.94(s), 8.92(s), 9.95(m), 10.13(m)μ, and by its hydrolysis to triphenylphosphine oxide, UVλ_{max}^{EtOH} : 255, 265.5, 272.5mμ.

The cloudy benzene solution on standing overnight deposited more hydroxytriphenylphosphonium bromide as yellow needles which were collected on a tared fritted glass funnel under nitrogen, wt. 2.29 g., and identified as above. The total weight of hydroxytriphenylphosphonium bromide obtained was 2.45 g., 6.83mmoles, 39% - fumes strongly in air.

To the residual benzene solution was added 5 ml. of water and after thorough shaking the wet benzene was flash distilled. TLC (solvents A & D) of the residual brown liquid gave spots for bromoisobutyrophenone, isobutyrophenone and triphenylphosphine oxide. n-Hexane was then added precipitating a brown solid, wt. 3.90 g., m.p. 123-142°; IR($CHCl_3$): cf. triphenylphosphine oxide; purified by solution in refluxing methanol, evaporation of the solvent and recrystallization from n-hexane-benzene (8:1) to give pure triphenylphosphine oxide, white prisms, wt. 2.45 g., (50%), m.p. and m.m.p. 153-158°.

The n-hexane solution was concentrated by distillation (orange color seen in joints of receiver flasks) through a 7 cm. Vigreux column and the residual yellow liquid was distilled from a 10 ml. oil-jacketed flask giving 2.42 g., of yellow-green distillate, boiling range about 100-115° (12-13 mm.). TLC (solvent A) gave a faint spot for α-bromoisobutyrophenone ($UV_{\lambda max}^{EtOH}$: 252.5 mμ) and a large strong spot whose R_f value matched isobutyrophenone ($UV_{\lambda max}^{EtOH}$: 244mμ, top half of spot, and $UV_{\lambda max}^{EtOH}$: 242.5 mμ, bottom half of spot). IR (CCl_4): 5.92 and 6.01 μ. NMR ($CDCl_3$): signals at 1.17 and 1.07 (CH_3- of isobutyrophenone), 1.95 (CH_3- of α-bromoisobutyrophenone), 2.0 δ (CH_3- of α-methacrylophenone) and signals at 5.45 and 5.75 δ and multiplets at 7.1-7.5 δ and 7.6-8.0 δ . Integration revealed that the ratio of isobutyrophenone: α — methacrylophenone:α-bromoisobutyrophenone was 73:25: ca. 2. On this basis, the approximate yields of the ketonic products are: isobutyrophenone, (1.78 g., 12 mmoles,68%); α-methacrylophenone, (0.61 g., 4.17 mmoles,21%) and α-bromoisobutyrophenone, (ca. 0.03 g., 0.13 mmole, less than 1%).

B. <u>In Methanol-Benzene</u>:

In 40 ml. of benzene and 8 ml. methanol was refluxed a mixture of bromoisobutyrophenone (3.00 g., 13.2 mmoles) and triphenylphosphine (3.50 g., 13.3 mmoles) for 23 hrs.

The solvents were distilled and n-hexane was added to the residual semi-solid. The n-hexane-insoluble material was collected and triturated with benzene. Methyltriphenylphosphonium bromide (0.64 g., 1.79 mmoles, 13%), m.p. 215-230° was obtained as a benzene-insoluble white powder and identified by IR($CHCl_3$). Evaporation of the benzene gave 3.32 g. of crude triphenylphosphine oxide which was recrystallized from n-hexane giving 3.05 g., 11 mmoles, 83% of pure material m.p. and m.m.p. 154-159°.

The original n-hexane reaction solution by TLC (solvent A) gave only a spot corresponding to isobutyrophenone. V.p.c. (20% Carbowax), however, showed an unresolvable shoulder on the isobutyrophenone peak and the IR spectrum confirmed the presence of α-methacrylophenone by giving a small shoulder at 6.0µ on the carbonyl peak (5.92µ) of isobutyrophenone. After distillation as in A, an almost colorless liquid, 1.50 g., was obtained, b.p. 100-130° (16 mm.). NMR (neat) indicated that the ratio of isobutyrophenone to α-methacrylophenone was 85:15. Therefore, the yields are: isobutyrophenone (1.27 g., 8.61 mmoles, 65% actual yield or 75%

yield based on available triphenylphosphine); α-methacrylophenone (0.23 g., 1.58 mmoles, 12% actual yield or 14% yield based on available triphenylphosphine).

C. <u>In Methanol-Benzene Using Excess Triphenylphosphine</u>:

A mixture of bromoisobutyrophenone (2.00 g., 8.8 mmoles) and triphenylphosphine (5.23 g., 19.9 mmoles) was refluxed in 70 ml. of benzene and 9 ml. of methanol for 20.5 hrs. Methyltriphenylphosphonium bromide (2.68 g., 7.51 mmoles, 38% yield, based on triphenylphosphine), m.p. 225-234° and triphenylphosphine oxide (2.15 g., 7.74 mmoles, 39% yield based on triphenylphosphine) m.p. 147-155°, were isolated as in B. After distillation of the solvent, the residue was dissolved in $CHCl_3$ and transferred to a 25 ml. oil — jacketed flask. The fraction with b.p. 95-110° (about 12 mm) was collected, wt. 1.26 g. and its IR and NMR spectra (CCl_4) were identical with those of authentic isobutyrophenone (8.52 mmoles, 97%). The residue of the distillation solidified. Trituration with n-hexane gave more triphenylphosphine oxide (0.31 g., 1.1 mmoles, 6% yield based on triphenylphosphine) and evaporation of the n-hexane left white crystals, triphenylphosphine (0.53 g., 2.02 mmoles, 10% recovery), identified by IR ($CHCl_3$).

D. <u>In Refluxing Acetonitrile</u>:

A mixture of α-bromoisobutyrophenone (3.117 g., 13.75 mmoles) and triphenylphosphine (3.838 g., 14.65 mmoles) was refluxed in 100 ml. of acetonitrile for 20.5 hrs. The solvent was distilled and the residue extracted with ethyl acetate. The brown insoluble solid which remained was dissolved in hot methylene chloride-ethyl acetate (charcoal) giving a yellow solution. On cooling, (2-benzoylpropyl)triphenylphosphonium bromide, crystallized as a white solid, wt. 3.21 g., 6.57 mmoles, (48%), m.p. 215-224°. An analytical sample, obtained after three recrystallizations from acetonitrile-ethyl acetate melts at 223.5-225.5° (after drying for 12 hrs. in an Abderholden pistol (at 0.1 mm.) over P_2O_5 with refluxing toluene.

<u>Analysis</u> calcd. for $C_{28}H_{26}BrOP$: C,68.72%; H,5.36%

Found: C,68.73%; H,5.08%.

NMR($CDCl_3$): Multiplet at 7-8.0 δ (phenyl absorption), a broad series of peaks 3.6-4.6 δ ($-CH_2CH-$) and a split doublet centered at 1.65 δ (CH_3-).

A comparison of the IR spectrum with that of the genuine salt, whose synthesis is described in section H, showed the two spectra to be identical.

Evaporation of the methylene chloride - ethyl acetate solution yielded triphenylphosphine oxide (0.29 g., 1.04 mmoles, 7%), identified by its IR spectrum (CH_2Cl_2).

The original ethyl acetate solution was distilled and 60-70° petroleum ether added to the yellow residue. Cooling in ice yielded a partly crystalline material, crude triphenylphosphine oxide, ca. 1.7 g., 6.1 mmoles, with melting range 110-150°; IR bands ($CHCl_3$): 6.96(s), 8.50(P-O) and 8.98μ.

The petroleum ether, in turn, was distilled and yellow liquid residue further distilled from oil-jacketed flask to give 0.80 g., of colorless liquid, b.p. 110-120° (12-13 mm); IR(CCl_4): 5.92 and 6.02μ; v.p.c. (20% Carbowax): unresolvable shoulder on isobutyrophenone peak; NMR spectrum (CCl_4):

multiplet 7.3-7.9, doublet 5.5 and 5.75, (methylene) multiplet centered at 3.5, singlet 2.0 (CH_3- of α-meth-acrylophenone) and strong doublet 1.1 and 1.2 δ (CH_3- of isobutyrophenone). Integration indicated that the ratio of isobutyrophenone to α-methacrylophenone was 70:30. Therefore, the approximate yields are: isobutyrophenone (0.56 g., 3.78 mmoles, 29%) and α-methacrylophenone (0.24g., 1.64 mmoles, 13%).

E. <u>In Acetonitrile at 25°</u>:

(a) A mixture of bromoisobutyrophenone (3.010 g., 13.2 mmoles) and triphenylphosphine (3.499 g., 13.3 mmoles was stirred for 43 hrs. at room temperature (25°) in 30 ml. acetonitrile. The resultant clear yellow-green solution was cooled in ice water and the solvent distilled using a vacuum pump. Benzene was added to the residual semi-solid and an insoluble powder, which fumed strongly in air, was collected in a fritted glass funnel under nitrogen. An attempt to take its NMR spectrum was unsuccessful as material was not sufficiently soluble at room temperature in either deuterochloroform or methylene dichloride. TLC (solvent D) gave only one spot; same R_f as triphenylphosphine oxide. TLC (solvent A) of the benzene solution gave spots for the starting materials and for isobutyrophenone and triphenylphosphine oxide. The benzene was distilled and a few ml. of carbon tetrachloride was added to the residue. The yellow-green solution obtained was decanted and examined by NMR. The spectrum showed a strong peak at 1.96 (CH_3- of α-bromoisobutyrophenone) and a small doublet at 1.08 and 1.18 (CH_3- groups of isobutyrophenone). No olefinic H's seen. Integration indicated that the ratio of α-bromoisobutyrophenone to isobutyrophenone is 78:22. The IR spectrum confirmed the absence of α-methacrylophenone.

The carbon tetrachloride-insoluble hygroscopic solid yielded only triphenylphosphine oxide on standing (identified by IR spectrum and m.p.).

(b) When the same quantities of α-bromoisobutyrophenone and triphenylphosphine were stirred for 96 hrs. at room temperature in 35 ml. of acetonitrile, the solvent distilled as in (a), and diethyl ether added to the residue, a hygroscopic powder was again obtained, collected under a nitrogen atmosphere, and placed directly in an NMR tube. NMR ($CDCl_3$): a multiplet at 1.5-1.7 δ (CH_3- group of (2-benzoylpropyl) triphenylphosphonium bromide) and a quintet at 1.05-1.30 δ (CH_3-group of the O-phosphonium(salt)? However, both multiplets were very small (integrated areas 3.0 and 5.2, respectively) with respect to aromatic H's cluster at 7.4-8.0 δ (integrated area 55.8). Therefore, major product is apparently again a complex mixture of triphenylphosphine oxide-triphenylphosphine.

From the original ethereal solution was crystallized about 1.0 g., of white solid, m.p. 110-140°. IR($CHCl_3$): 8.51(w) $[-P{\rightarrow}O]$,8.91μ(vs) $[(C_6H_5)_3P-]$, no carbonyl bands; NMR($CDCl_3$): a multiplet centered at 7.46 δ and a broad singlet at 14.1 δ (H-bonded phenolic H's identified in this region(61)). The spectral evidence points to another complex mixture of triphenylphosphine-triphenylphosphine oxide.

The ether was evaporated and a portion of the residue dissolved in carbon tetrachloride. NMR of this solution indicated that the ratio of α -bromoisobutyrophenone to isobutyrophenone is 62:38. No traces of α -methacrylophenone by either NMR or IR. The other component of the residue is triphenylphosphine oxide, identified by IR($CHCl_3$).

F. In Diethylmalonate:

A mixture of α-bromoisobutyrophenone (4.00 g., 17.6 mmoles) and triphenylphosphine (4.87 g., 18.6 mmoles) was heated at 110° (oil bath) in diethylmalonate (25.0 g., 0.154 mole) for 34 hrs. Insoluble material (5.41 g.) was removed and extracted in a Soxhlet apparatus with 150 ml. benzene for 22 hrs. The benzene-insoluble tan powder, left in Soxhlet cup, was identified as (2-benzoylpropyl)triphenylphosphonium bromide (3.83 g., 7.84 mmoles, 45%), m.p. 210-220°. Two recrystallizations from aqueous ethanol (charcoal) gave a light yellow solid, m.p. 222-226°. The infrared spectrum (CH_2Cl_2) of both the crude and the recrystallized material was identical with that of the authentic salt. The benzene solution was evaporated and the black oily residue extracted with 60-70° petroleum ether. Partial distillation of the petroleum ether precipitated 0.05 g. of triphenylphosphine oxide, m.p. 148-157° and total evaporation left a green liquid to which was added 30 ml. of 2,4-dinitrophenylhydrazine (Brady's) solution. An orange precipitate was obtained, 0.12 g., 0.37 mmoles, 2%, which gave one spot on TLC (solvent A) and had the same R_f value as authentic 2,4-DNP of isobutyrophenone.

Distillation of the original diethylmalonate solution yielded a colorless liquid, wt. 19.98g., b.p. 92-94° (16-17 mm.). The percentage of isobutyrophenone, whose presence was detected by TLC (solvent A), was determined by UV from the intensity of the maximum at 243 mμ(EtOH). It was found that 3% of the solution or 0.60 g. is isobutyrophenone (4.05 mmoles, 23%). The black-brown semi-crystalline distillation residue was extracted with 80 ml. of 60-70° petroleum ether. Distillation of the solvent left an orange oil to which was added 60 ml. of 2,4-DNPH solution. The orange precipitate, ca. 0.60 g., was recrystallized from ethyl acetate to yield 0.42 g., 1.28 mmoles, 7% of 2,4-DNP of isobutyrophenone, m.p. and m.m.p. 158.5-162°.

The petroleum ether-insoluble dark-brown material was sublimed at 210° (0.75 mm.) for 30 hrs. The yellow crystals obtained, 1.97 g., were washed with 10 ml. diethyl ether giving pure triphenylphosphine oxide (1.86 g., 6.69 mmoles, 38%), m.p. and m.m.p. 154-157°. The ether solution contained a mixture of triphenylphosphine oxide and triphenylphosphine.

G. Synthesis of α-Methacrylophenone:

According to the method of Stevens and Etling,(36) to α-bromoisobutyrophenone (7.95 g., 0.035 mole) dissolved in 25 ml. of benzene was added 25 ml. of dry triethylamine and 3 ml. of dry pyridine. After refluxing for 48 hrs., distillation gave faintly yellow liquid, 2.55 g., 50%, b.p. 103° (18 mm.); IR(CCl_4): 6.01μ; UVλ_{max}^{EtOH} : 245 mμ; TLC (solvent A): same R_f value as isobutyrophenone.

H. Synthesis of (2-Benzoylpropyl)triphenylphosphonium bromide:

Into a mixture of α-methacrylophenone (0.46 g., 3.15 mmoles) and triphenylphosphine (0.825 g., 3.15 mmoles) in 15 ml. of refluxing xylene was slowly bubbled hydrogen bromide for 1 hr. The precipitate was washed with benzene leaving 1.429 g. of yellow crystals. The colored impurities were extracted with boiling ethyl acetate and the residual white powder was dried overnight in a vacuum desiccator over calcium chloride to yield 1.21 g., 2.47 mmoles, 79%, m.p. 223-227.5°.

Structure confirmed by NMR ($CDCl_3$): Multiplet 7-8.0 δ (relative intensity 20.6), broad series of signals near 4.0 δ (relative intensity 3.3) and a split doublet centered at 1.65 δ (relative intensity 3.0).

I. Control Experiments:

(a) α-Bromoisobutyrophenone (0.503 g., 2.2 mmoles) was recovered unchanged (TLC: solvent A) after refluxing in 10 ml. of acetonitrile for 24 hrs.

(b) α-Bromoisobutyrophenone (1.003 g., 4.4 mmoles) was refluxed in a mixture of 15 ml. of benzene and 3 ml. of methanol for 24 hrs. No evidence of any dehalogenation or dehydrohalogenation was found by TLC(Solvent A). Triphenylphosphine oxide (1.226 g., 4.4 mmole) was added and the solution was refluxed another 24 hrs. TLC (solvents A and D) indicated that only α-bromoisobutyrophenone and triphenylphosphine oxide were present.

(c) (2-Benzoylpropyl)triphenylphosphonium bromide (0.502 g., 1.02 mmoles) was refluxed in 10 ml. methanol for 24 hrs. TLC (solvent A): no decomposition products seen. The solvent was evaporated leaving 0.51 g., white crystalline material, m.p. 217-224°;IR(CH_2Cl_2) identical with IR spectrum taken before refluxing.

Reaction of α-Chlorodeoxybenzoin with Triphenylphosphine:

A. In Benzene:

A mixture of α-chlorodeoxybenzoin (11.30 g., 0.0491 mole) and triphenylphosphine (13.10g.,0.050 mole) was refluxed in 135 ml. of dry benzene for 20 hrs. The yellow-green solution obtained was divided into two equal volumes, (1) and (2), of 83 ml. each:

(a) Attempted isolation of products by method of Trippett-Walker:$^{(9)}$

Solution (1) was evaporated to dryness on a flash evaporator leaving a residue of 12.47 g. of yellow-green viscous oil which was extracted with 350 ml. of hot 60-80° petroleum ether. On cooling this solution, 0.81 of triphenylphosphine oxide, m.p. 145-157°, crystallized. Pure by TLC (solvent D). Evaporated of the petroleum ether gave 4.98 g., of yellow-green oil which by TLC (sovents A and D) was a five-component mixture and contained unreacted starting materials, diphenylacetylene, deoxybenzoin and the ylid. The petroleum ether insoluble cream solid, wt. 6.77 g., was by TLC (solvents A and D) a six-component mixture and contained in addition to the above α-phenylphenacyltriphenylphosphonium chloride.

(b) Isolation of products:

Solution (2) was evaporated to dryness and the residual oil was extracted with 250 ml. hot cyclohexane. On cooling triphenylphosphine oxide (2.50 g. after drying in air overnight, 9.0 mmoles) crystallized, m.p. and m.m.p. 150-157°. The cyclohexane solution was re-combined with the cyclohexane-insoluble brown solid and the solvent distilled on a flash evaporator. The residue was placed on a column (3 cm. in diameter) of 160 g. of acid washed alumina (Merck) with the aid of benzene and was eluted first with 400 ml. benzene and then with about 350 ml. 95% ethanol. The combined benzene fractions were evaporated to yield 4.35 g. of yellow-green oil. TLC (solvent A) gave spots for diphenylacetylene, α-chlorodeoxybenzoin and deoxybenzoin. This mixture, dissolved in benzene, was analyzed by v.p.c. on a 5' x 1/4" glass column of silicone gum rubber 5% SE-30 on 60/80 HMDS Chromasorb P at a column temperature of 198° and a flow rate of 64 cc/min. Calibration curves were made for each material by injecting benzene solutions of known concentrations on the same column at the same temperature, flow rate and attenuation and plotting the areas of the peaks vs. mg. material injected. The areas of the components in the unknown mixture were determined and compared to the appropriate calibration curve. It was found that the mixture contains 17% or 0.72 g. diphenylacetylene, 34% or 1.48 g., deoxybenzoin and 32% or 1.37 g. α-chlorodeoxybenzoin. The rest of the weight is due to benzene which was not completely removed by distillation.

Evaporation of the ethanolic chromatography fractions left 4.89 g. of a light tan solid which was extracted with hot cyclohexane. Cooling gave 1.41 g. of triphenylphosphine oxide, m.p. and m.m.p. 155.5-159°. TLC (solvent D) indicated that both the cyclohexane solution and the cyclohexane insoluble material were mixtures of triphenylphosphine oxide and α-phenylphenacyltriphenylphosphorane. The mixtures were combined and the solvent evaporated to dryness. IR ($CHCl_3$) of the residual solid, 2.70 g., confirmed the TLC results by showing triphenylphosphine bands at 8.49, 9.12, and 9.71μ and ylide bands at 6.66, 6.72, 7.21 and 10.32μ; no carbonyl bands. The percentage of ylide in the mixture was determined by the UV from the intensity of ylide absorption peak at 320mμ (ϵ = 7200). [Triphenylphosphine oxide shows no absorption above 300mμ]. A methanolic solution, apparent molarity in ylide = 3.60×10^{-4}, gave an absorbance of 0.95 at 320mμ or an apparent ϵ value of 2650 for the ylide. From this it follows that $^{2650}/7200 \times 100$ or 37% of the mixture is ylide. This corresponds to 1.0 g. of ylide.

The multicomponent fractions of solution (1) were combined and refluxed briefly (ca. 15 min.) with 125 ml. ethyl acetate. The insoluble α-phenylphenacyltriphenylphosphonium chloride was collected as a white powder which after drying in vacuum desiccator overnight weighed 1.448 g., m.p. 239-241°.

Anal. Calcd. for $C_{32}H_{26}ClOP$: C,77.96%; H,5.32%; Cl,7.19%

Found: C,78.24%; H,5.47%; Cl,7.17%.

IR bands (KBr): 6.0(s),6.95(s),7.74(m),8.21(m),9.06(s),10.05 (m)μ. NMR($CDCl_3$): Three distinct groups of multiplets 7-8.5 δ , a doublet centered at 9.64 δ (J_{pH}=12.5cps)-aliphatic H: confirmed by D_2O exchange.

Summary of overall yields:

Diphenylacetylene (1.48 g., 8.32 mmoles, 17%); deoxybenzoin (3.02 g., 15.4 mmoles, 31%); α-chlorodeoxybenzoin (2.80 g., 12.1 mmoles, 25%); triphenylphosphine oxide (11.3 g., 40.7 mmoles, 82%); α-phenylphenacyltriphenylphosphonium chloride (2.90 g., 5.88 mmoles, 12%); α-phenylphenacyltriphenylphosphorane (2.0 g., 4.37 mmoles, 9%).

B. In Benzene-Methanol:

A mixture of α-chlorodeoxybenzoin (3.000 g., 13.0 mmoles) and triphenylphosphine (3.427 g., 13.1 mmoles) was refluxed in benzene (40 ml.) - methanol (5 ml.) for 24 hrs. Since TLC (solvents A and D) indicated that no phosphonium salt had formed, most of the solvent was evaporated and residual solution chromatographed on a 3 cm. diameter column containing 150 g. acid washed aluminum oxide (Merck). Eluted first with 400 ml. benzene, the fractions combined and bulk of the solvent evaporated. To the turbid residual solution was added 95% ethanol giving a clear yellow-green solution (25.69 g.). TLC (solvent A) indicated that the solution contained triphenylphosphine, α-chlorodeoxybenzoin, deoxybenzoin and traces of diphenylacetylene. Solution injected on glass v.p.c. column (5% SE-30, 60/80 HMDS, Chromasorb P, at 197° and flow rate 65 cc/min.). It was found that the total solution contained (1.80 g., 9.2 mmoles, 69%) of deoxybenzoin; (0.34 g., 1.48 mmoles, 11%) of α-chlorodeoxybenzoin and (ca. 0.05 g., ca. 0.28 mmole, ca. 2%) diphenylacetylene. Triphenylphosphine gave a misshapen small peak but, in general, behaved erratically on the column. Hence, its yield could not be determined.

Elution of the alumina column with 200 ml. 95% ethanol and evaporation of the solvent from the fraction, gave 2.86 g. of solid, very broad m.p. TLC (solvent D) gave spots for the ylide (α -phenylphenacyltriphenylphosphorane) and triphenylphosphine oxide. Analyzed by UV as in A. A solution, apparent molarity in ylide of 5.28 x 10^{-4}, gave an absorbance of 0.79 at 320 mμ, indicating that 21%, of the solid was ylide; overall yield of ylide (0.60 g., 1.31 mmoles, 12%); triphenylphosphine oxide (2.26 g., 8.13 mmoles, 63%).

C. In Acetonitrile:

A mixture of α-chlorodeoxybenzoin (1.32 g., 5.74 mmoles) and triphenylphosphine (1.59 g., 6.07 mmoles) was refluxed in 40 ml. of acetonitrile for 24.5 hrs. The solvent was evaporated and 45 ml. of benzene added to the residue. The benzene extracts were decanted, and the insoluble tan tacky semi-solid was dissolved in methylene dichloride. After standing overnight, the solvent methylene dichloride was evaporated leaving 0.51 g. of gray solid which was a mixture of α-phenylphenacyltriphenylphosphonium chloride and the ylide (α-phenylphenacyltriphenylphosphorane) by TLC (solvent E). Identification confirmed as follows: a portion ot the solid was dissolved in hot ethyl acetate - chloroform and on cooling a white crystalline material, pure phosphonium salt, was obtained, 0.08 g., m.p. 239-240.5°, one spot, R_f 0.1, on TLC (solvent E). The solution was evaporated and residue extracted with hot cyclohexane. Removal of the cyclohexane on a flash evaporator left 0.05 g. of ylide as a faintly yellow solid, $UV_{\lambda max}^{EtOH}$: 259.5, 266, 273, and 327 mμ. TLC (solvent E) gave one spot, R_f 0.5. The cyclohexane insoluble material by TLC (solvent E) gave 2 spots, R_f's 0.1 and 0.5. The total weight of 0.51 g. corresponds to a yield of 18-19% (with the first value gotten by assuming all material is the phosphonium salt and the second by assuming all is ylide).

The original benzene extracts were evaporated and the glassy semi-solid residue chromatographed through a 3 cm. diameter column packed with 100 g. neutral aluminum oxide (Brinkmann). Eluted first with 450 ml. benzene and the solvent evaporated leaving 0.78 g. of brownish oil, by TLC (solvent A) a mixture of diphenylacetylene, α-chlorodeoxybenzoin, and deoxybenzoin. The percentage of the acetylenic component was determined by UV from the intensity of the diphenylacetylene peak at 297mμ (ϵ =31,100) [neither of the other components gave any significant absorption in this region at the concentrations used]. A 7.27×10^{-5} M (apparent molarity in diphenylacetylene) ethanolic solution was used and at 297mμ an ϵ value of 8.7×10^3 was obtained indicating that the mixture contained 28% diphenylacetylene (0.21 g., 1.18 mmoles, 21%).

The percentage of α-chlorodeoxybenzoin was determined by halogen analysis. Found: 2.41% chlorine; calcd. 15.37% chlorine, in pure α-chlorodeoxybenzoin. Therefore, the mixture contains 16% α-chlorodeoxybenzoin (0.12 g., 0.52 mmole, 9% recovery). By difference, the yield of deoxybenzoin is 0.44 g., 2.24 mmoles, 39%.

Elution of the column with 180 ml. ethanol and evaporation of the solvent gave as a partly crystalline material, triphenylphosphine oxide (by TLC: solvent A) containing traces of ylide. This was dissolved in the minimum volume of boiling cyclohexane. On cooling, light yellow crystals were obtained; 1st crop 1.08 g., m.p. 137-145°, m.m.p. with triphenylphosphine oxide 137-149°, (UV revealed that the impurity is traces of ylide), 2nd and 3rd crops 0.12 g., colorless needles, m.p. and m.m.p. 153-158° (TLC, solvent E-one spot, same R_f as authentic triphenylphosphine oxide). The cyclohexane was evaporated leaving 0.05 g. of solid which by TLC (solvent E) was mostly triphenylphosphine oxide. Total yield triphenylphosphine oxide is 1.20 g., 4.32 mmoles, 75%.

D. <u>In Benzene-Diethylmalonate</u>:

α-Chlorodeoxybenzoin (3.50 g., 15.2 mmoles) and triphenylphosphine (4.22 g., 16.1 mmoles) were dissolved in a mixture of diethylmalonate (10.00 g., 62.5 mmoles) - benzene (10 ml.) and heated at 110° (oil bath) for 16 hrs. The black-brown solution was directly distilled at reduced pressure from an oil-jacketed flask and the following fractions were taken:

Fraction No. 1: a colorless liquid, 2.67 g., oil temperature up to 85° (17 mm.); TLC (solvent A) gave only a spot for diethylmalonate.

Fraction No. 2: a light yellow liquid, 9.27 g., oil temperature 86-200°; (0.15 mm); TLC (solvent A) gave spots for diphenylacetylene, deoxybenzoin, diethylmalonate and triphenylphosphine oxide.

Fraction No. 3: a yellow oil, 3.36 g., which solidified in side-arm of distilling flask; oil temperature 210-240° (0.15 mm.); TLC (benzene) on an alumina plate indicated that the material was mostly triphenylphosphine oxide Traces of diphenylacetylene and deoxybenzoin were also seen. The distillation residue was a black tar.

Fraction No. 2 was analyzed by v.p.c. on a 6' x 1/4" column of silicone gum rubber 5% SE-30 on 60/80 mesh HMDS, Chromasorb P. The column temperature was programmed to rise from 140-280° in 10 minutes and the flow rate was 80 ml. /min. Yields: diphenylacetylene (1.00 g.), deoxybenzoin (1.10 g.) and triphenylphosphine oxide (0.08 g.) UV analysis indicated(by measurement of the intensity of the 297 mμ maximum) that ca. 10% of fraction No. 2 or 0.93 g. is diphenylacetylene.

Fraction No. 3 was also analyzed by v.p.c. on the same column. The column temperature was programmed to rise from 140-300° in 10 minutes and the flow rate was 80 ml./min. It was found that ca. 3% or 0.1 g., is diphenylacetylene and ca. 2% or 0.07 g. is deoxybenzoin. The rest of the material, 3.2 g., is triphenylphosphine oxide. UV analysis indicated (the intensity of the maximum at 297mμ was measured) that ca. 2% of fraction No. 3 or 0.07 g. is diphenylacetylene.

Overall yields of products obtained: diphenylacetylene (1.1 g., 6.18 mmoles, 40%); deoxybenzoin (1.2 g., 6.12 mmoles, 40%) and triphenylphosphine oxide (3.3 g., 11.9 mmoles, 78%).

Stability of α-Phenylphenacyltriphenylphosphorane in Refluxing Acetonitrile:

The above ylide (0.253 g., 0.55 mmole) was refluxed under nitrogen atmosphere in 10 ml. of acetonitrile for 24 hrs. TLC (solvents A and D) gave only one spot and showed no evidence of any decomposition to deoxybenzoin and triphenylphosphine oxide. Evaporation of the light yellow solution to dryness left a faintly yellow solid (0.25 g., 100% recovery), m.p. 187-194° [starting material m.p. 190-195°].

Stability of α-Phenylphenacyltriphenylphosphonium Chloride in Refluxing Acetonitrile:

The salt (0.301 g., 0.61 mmole) was refluxed in 10 ml. acetonitrile for 24 hrs. Solvent was evaporated and the residual white solid dried at 110°, wt. 0.31 g. (100% recovery), m.p. 233-238°, IR($CHCl_3$) identical with spectrum obtained before reflux; no evidence of any formation of ylide.

Reaction of α-Bromodeoxybenzoin with Triphenylphosphine:

A. In Benzene:

A mixture of α-bromodeoxybenzoin (2.00 g., 7.27 mmoles) and triphenylphosphine (2.02 g., 7.69 mmoles) was refluxed in 55 ml. of benzene for 23 hrs. Insoluble white solid (2.70 g.) was collected by filtration and extracted in a Soxhlet apparatus with 130 ml. of benzene for 3.5 hrs. Benzene-insoluble material, left in Soxhlet cup, was identified as α-phenylphenacyltriphenylphosphonium bromide (1.56 g., 2.9 mmoles, 40%), m.p. 239.5-241° dec. The analytical sample was recrystallized once from aqueous ethanol, m.p. 243-244° dec.

Anal. calcd. for $C_{32}H_{26}BrOP$: C,71.51%; H,4.88%

Found: C,71.72%; H,5.08%.

IR bands (KBr): 6.08s), 6.97(s), 7.81(m), 8.30(m), 9.18(s), 10.06(m)μ.

NMR($CDCl_3$): Three distinct groups of multiplets at 7.0-8.5 δ (aromatic H's) and a doublet centered at 8.96 δ (J=12.5cps).

Extracted by boiling benzene but precipitated from warm benzene gave 1.3 mmoles, 0.70 g., 18% more of the phosphonium bromide, m.p. 223-241° one spot on TLC (solvent E) and IR ($CHCl_3$): identical with analytically pure phosphonium salt. The benzene extracts were evaporated, the residue washed with dilute sodium hydroxide solution and the oily material extracted into hot cyclohexane. Cooling gave crystals of triphenylphosphine oxide (0.41 g., 1.48 mmoles, 20%), identified by TLC (solvent D) and IR($CHCl_3$).

The benzene reaction solution was evaporated, triturated with 50 ml. of 60-70° petroleum ether and the white insoluble powder dissolved in hot cyclohexane. On cooling, triphenylphosphine oxide, white needles, was obtained (0.32 g., 1.15 mmoles, 16%), m.p. 149-155°, identified by IR($CHCl_3$).

The petroleum ether was evaporated leaving oily semi-solid, by TLC (solvent A) a mixture of diphenylacetylene, deoxybenzoin and triphenylphosphine oxide. The percentage of diphenylacetylene was obtained by UV from the intensity of the max. at 297mμ and was found to be 7% or 0.05 g., 0.28 mmole, (4% overall yield). The percentage of deoxybenzoin was determined by dissolving the semi-solid in ethanol and adding 30 ml. of 2,4-dinitrophenylhydrazine Brady's solution. The orange-yellow precipitate was collected and dried overnight in a vacuum desiccator over calcium chloride to give 0.77 g. of 2,4-dinitrophenylhydrazone

(one spot by TLC: solvent A). The minimum yield of deoxybenzoin, therefore, is 0.40 g. (28%). Since the average recovery of authentic benzyl phenyl ketone by formation of the 2,4-DNPH is 80%, the adjusted yield is 0.50 g. (35%). Therefore, yield of triphenylphosphine oxide is 0.15 g.(7%) or a total of 43%.

B. In Benzene-Methanol:

A mixture of α-bromodeoxybenzoin (3.002 g., 10.9 mmoles) and triphenylphosphine (2.886 g., 11.0 mmoles) was refluxed in benzene (40 ml.)-methanol (5 ml.) for 23 hrs. TLC (solvent A) of the yellow clear solution indicated that only deoxybenzoin and triphenylphosphine oxide were present. After evaporation of the solvent, the residue was chromatographed on a 3 cm. diameter column (150 g. acid washed alumina). Elution with benzene (350 ml.) gave 2.23 g. of yellow solid which by v.p.c. (glass 5% SE-30, 196°, 64 cc/min.) was pure deoxybenzoin (11.2 mmoles, ca. 100% yield). Elution with 95% ethanol (200 ml.) gave white crystals, 3.28 g., which after drying overnight in a vacuum desiccator weighed 3.03 g., m.p. 149-157°. TLC (solvent D) and IR ($CHCl_3$) indicated that the material is pure triphenylphosphine oxide (10.9 mmoles, ca. 100% yield).

C. In Acetonitrile:

A mixture of α-bromodeoxybenzoin (2.999 g., 10.9 mmoles) and triphenylphosphine (3.093 g., 11.8 mmoles) was refluxed in 70 ml. of acetonitrile for 22.5 hrs. The viscous oil left after removal of solvent, was extracted first with 60-70° petroleum ether, then with benzene and finally with hot ethylacetate. The insoluble residue, a yellow powder, 0.23 g., is crude α-phenylphenacyltriphenylphosphonium bromide, identified by IR($CHCl_3$). The ethyl acetate extracts were evaporated and the orange-red residual oil treated with aqueous sodium sulfite. The yellow solid obtained was extracted into 250 ml. benzene, the benzene solution dried over anhydrous magnesium sulfate and then evaporated to dryness leaving 1.57 g. of yellow-green oil (a) which by TLC (solvent D) contained ylide, (UV λ_{max}^{EtOH}: 324, 274 and 267 mμ) triphenylphosphine oxide and traces of deoxybenzoin. Distillation of the petroleum ether extracts gave 0.76 g. oil, by TLC (solvent A) a mixture of diphenylacetylene and deoxybenzoin.

Evaporation of most of the benzene solution left a yellow oil (b), wt. 3.29 g., which was combined with oil (a) and then chromatographed on a column (5 cm.in diameter) of 300 g. acid washed aluminum oxide (Merck). Elution with 600 ml. benzene and evaporation of the solvent, gave 1.36 g. of oil, by TLC (solvent A) a mixture of diphenylacetylene and deoxybenzoin. Elution with 250 ml. ethanol gave 3.51 g. of yellow semi-solid, by TLC (solvent D) and IR ($CHCl_3$) a mixture of ylide and triphenylphosphine oxide.

The fractions which contained only diphenylacetylene and deoxybenzoin were combined, wt. 2.12 g., and dissolved in benzene to yield 15.01 g. of solution (sp.gr.0.905 g./ml.). V.p.c. (glass 5%SE-30 column, at 198°, flow rate 65 cc/min.) indicated that 5% of the solution or 0.75 g. was diphenylacetylene and 4.5% or 0.66 g. was deoxybenzoin. Overall yields are: diphenylacetylene 4.21 mmoles, (39%); deoxybenzoin 3.37 mmoles, (1%).

The percentage of ylide in the second mixture was determined by UV from the intensity of the 320mμ peak of the ylide spectrum. A 3.57 $\times 10^{-4}$ M solution (apparent molarity in ylide) gave an absorbance of 0.92 indicating that 37% of the mixture or 1.30 g., 2.84 mmoles, (26%) is ylide (α-phenylphenacyltriphenylphosphorane). The yield of triphenylphosphine oxide is 2.21 g., 7.95 mmoles, (73%).

D. <u>In Diethylmalonate - Benzene:</u>

A mixture of α-bromodeoxybenzoin (2.32 g., 8.45 mmoles) and triphenylphosphine (2.36 g., 8.96 mmoles) in a solution of benzene (10 ml.) - diethylmalonate (6.29 g., 39.3 mmoles) was heated at 110° (oil bath). At the end of 3 hrs. so much solid had accumulated that the magnetic stirrer stopped. The cream insoluble material (3.28 g.) was collected and extracted in a Soxhlet apparatus with 200 ml. of benzene for 5.5 hrs. The benzene-insoluble material, left in Soxhlet cup, was identified as α-phenylphenacyltriphenylphosphonium bromide (2.44 g.), m.p. 222-238° dec. From the warm benzene extracts precipitated 0.35 g. more of the salt. Total yield is, 2.79 g, 5.2 mmoles, (62%). IR spectrum (KBr pellet) was identical with that of analytically pure salt. Evaporation of the yellow benzene solution left a tan semi-solid, 0.32 g., which by TLC (solvent D) appeared to be mostly triphenylphosphine oxide plus traces of ylide and starting materials.

The volume of the original reaction solution was reduced by distillation of the benzene at atmospheric pressure. The residual red-brown liquid (7.35 g.) was analyzed by v.p.c. on a 6' x 1/4" column of silicone gum rubber 5% SE-30 on 60/80 mesh HMDS, Chromasorb P. The column temperature was programmed to rise from 150-300° in 10 min. and the flow rate was 120 ml./min. The following percentages were found: deoxybenzoin (7%), triphenylphosphine oxide (8%), and diphenylacetylene (ca. 1%). The overall yields are: deoxybenzoin (0.51 g., 2.6 mmoles, 31%), diphenylacetylene (0.07 g., 0.39 mmoles, 5%); triphenylphosphine oxide (0.59g., 2.12 mmoles, 25%).

Phenacyltriphenylphosphorane:

According to the method of Ramirez and Dershowitz,(26) phenacyltriphenylphosphonium bromide (2.0 g., 4.3 mmoles) upon stirring in 110 ml. of 5% aq. sodium hydroxide solution at 85° for 1.3 hrs. gave 1.07 g., 2.81 mmoles, (65%) of ylide, m.p. 183-185° [m.p. lit.(26) 178-180°] .

α-Methylphenacyltriphenylphosphorane:

According to the method of Dombrovskii and Shevchuk(60), from α-methylphenacyltriphenylphosphonium bromide (6.8 g., 0.014 mole) and sodium methoxide gave 5.5 g., 13.9 mmoles (98%) of ylide, m.p. 161-163° (after one recrystallization from aqueous ethanol) [m.p. lit.(60) 159-160°].

α-Phenylphenacyltriphenylphosphorane:

According to an extension of the method of Dombrovskii and Shevchuk,(60) to a stirred solution of α-phenylphenacyltriphenylphosphonium bromide (2.00 g., 3.7 mmoles) in 25 ml. of methanol was added dropwise during 5 min. a solution of sodium methoxide (0.21 g., 3.9 mmoles) in 10 ml. methanol. After being stirred for additional 30 min. the solution was poured into 200 ml. of water. The white precipitate was left to settle overnight, collected, washed with water and recrystallized twice from ethyl acetate to give 1.5 g., 3.28 mmoles, (88%) of ylide, m.p. 195-197° [m.p. lit.(38) 192-194°]. UV $\lambda_{max}^{CH_3OH}$: 320(ϵ =7200), 275, 267.5, 262 mμ; IR ($CHCl_3$): 6.68(vs), 6.75(vs),6.95(s),7.23,8.85,9.04(s), 9.33, 9.73, 10.0, and 10.33μ; TLC(solvent D): R_f=0.74 vs.

0.59 for triphenylphosphine oxide.

Reaction of α,α-Dibromodeoxybenzoin with Triphenylphosphine:

In Xylene:

A mixture of α,α-dibromodeoxybenzoin (3.000 g., 8.47 mmoles) and triphenylphosphine(4.460 g., 17.0 mmoles) was refluxed in 85 ml. of xylene for 17 hrs. A complex series of color changes was observed. The insoluble material, ca. 2.08 g., was collected on a sintered glass funnel under nitrogen. It slowly turned yellow on standing but remained a powder. Its colorless water washings were very strongly acidic (Alkacid test paper). Its IR($CHCl_3$) showed strongest bands at 6.92, 8.91 and 9.02 (sh)μ-all indicative of ϕ_3P structure - and no bands in carbonyl region. UVλ_{max}^{EtOH}: 222.5, 259.5, 265.5, 272.5mμ $\boxed{\phi_3P\rightarrow O}$ and a shoulder in 280 - 300mμ region. NMR ($CDCl_3$): a multiplet 7.0-8.2 δ with strongest signal at 456 cps (7.59 δ) and a singlet at 778 cps (12.96 δ), in the ratio of ca. 21:1. All data suggest that the solid is a complex salt of triphenylphosphine. The xylene was distilled at reduced pressure (12mm.) and to the semi-solid residue was added 60-70° petroleum ether. The insoluble triphenylphosphine oxide (2.70 g., 9.72 mmoles, 113%) was collected and identified by IR($CHCl_3$). The petroleum ether was evaporated, the residual oil redissolved in small amounts of benzene and chromatographed on a 3 cm. diameter column packed with 150 g. acid washed aluminum oxide (Merck). Eluted first with 500 ml. benzene. Most of the benzene was then evaporated to leave 15.96 g. of yellow-green solution, which by TLC (solvent A) contained diphenylacetylene and much smaller amounts of α-bromodeoxybenzoin and deoxybenzoin. V.p.c. analysis on a 5' x 1/4" glass column of silicone gum rubber (5% SE-30 on 60/80 HMDS, Chromasorb P, column temperature 201°, flow rate 65 ml./min.) indicated that the solution contained 0.74 g., 4.16 mmoles, (49%) diphenylacetylene, ca. 0.03 g., ca. 0.15 mmole, (ca.2%) deoxybenzoin and 0.13 g., 0.47 mmole, (6%) α-bromodeoxybenzoin. Elution of the column with 250 ml. 95% ethanol and evaporation of the solvent gave 0.28 g., 1 mmole, of triphenylphosphine oxide - identified by IR($CHCl_3$).

Reaction of α,α-Dichlorodeoxybenzoin with Triphenylphosphine: In Xylene:

A mixture of α,α-dichlorodeoxybenzoin (3.000g., 11.3 mmoles) and triphenylphosphine (6.042 g., 23.0 mmoles) was refluxed in 85 ml. of xylene for 4 hrs. The white insoluble solid (3.11 g.) was collected on a sintered glass funnel under nitrogen. When exposed to moisture, this material decomposed into α-chlorodeoxybenzoin and triphenylphosphine oxide (TLC: solvent A). Dissolved in wet chloroform and the solvent evaporated. Addition of n-hexane to the residual solid gave 1.67 g. (6.01 mmoles) of triphenylphosphine oxide (identified by IR) and evaporation of the n-hexane yielded 1.33 g. of α-chlorodeoxybenzoin (5.75 mmoles, 51%) identified by TLC and IR (CCl_4).

The xylene was distilled at atmospheric pressure and residual oil triturated with 60-70° petroleum ether. The precipitated triphenylphosphine oxide was collected (3.28 g., 11.8 mmoles) and identified by IR($CHCl_3$). The petroleum ether solution, after reduction of volume, was chromatographed on a 2-cm. diameter column packed with 60 g. acid washed aluminum oxide (Merck). The material eluted with benzene (200 ml.) was shown by TLC (solvent A) to be mostly diphenylacetylene and triphenylphosphine plus traces of α-chlorodeoxybenzoin and deoxybenzoin. V.p.c. analysis on a 6' glass column of silicone gum rubber (5% SE-30 column temperature 198°, flow rate 65 ml./min.) gave the following yields: diphenylacetylene (0.62 g., 3.48 mmoles, 31%) and triphenylphosphine (ca.0.34 g., ca. 1.3 mmoles, ca. 6%). The peaks found at α-chlorodeoxybenzoin and deoxybenzoin retention times were too small to be evaluated. Elution of the alumina column with 200 ml. 95% ethanol and evaporation to dryness gave 0.62 g., 2.23 mmoles, more of triphenylphosphine oxide (identified by IR).

<u>Reaction of α,α-Dibromoacetophenone with Triphenylphosphine:</u>

<u>Without solvent:</u>

An intimate mixture of α,α-dibromoacetophenone (8.00g., 28.8 mmoles) and triphenylphosphine (15.20 g., 58 mmoles) was heated at 200° for 2 hrs. Nothing could be forced to distil from the dark red-brown mass (oil bath up to 170°) even at 0.1 mm. The material was transferred into a larger flask with the aid of 95% ethanol and after evaporation of the solvent, the residue was extracted with several hundred ml. of 60-70° petroleum ether. As the petroleum ether was allowed to evaporate in a beaker, long white needles of triphenylphosphine oxide (1.04 g., 3.7 mmoles) crystallized and were identified by IR($CHCl_3$) and TLC (solvent D). Evaporation of the petroleum ether left 2.01 g. of brown liquid. TLC (solvent A): one spot, R_f 0.64, UV$_{\lambda_{max}}^{EtOH}$: two broad but very intense maxima at 237 and 265 mμ, UV$_{\lambda\ max}^{n\text{-hexane}}$: same spectrum as in ethanol, IR(CCl_4) : 3.25, 6.28, 6.35, 6.72, 6.92(s), 6.95(s), 8.16, 8.27 (s), 8.95(s), 9.73, 11.25 (vs), 11.53; NMR(neat): a complex multiplet of about 20 peaks centered at 7.17 δ , a sharp high singlet at 6.90 δ , small singlet at 6.63 δ , and two very small doublets at 5.95, 5.91 δ and 5.64, 5.60 δ respectively. Chromatography of the oil on a column of neutral alümina (Brinkmann) and elution with 5:1 petroleum ether (60-70°)- benzene gave as a first fraction 0.67 g. of yellow oil whose NMR(neat) was the same as for unpurified material. Integration gave the ratio of multiplet: singlet at 6.90 δ : singlet at 6.63 δ as 24.4:3.5:1.

The original rubbery petroleum ether insoluble mass was triturated with 400 ml. of diethyl ether to yield a tan powder, 10.86 g. TLC (solvent D): streaked on the plate but bulk of material had R_f value lower than that of triphenylphosphine oxide: IR ($CHCl_3$): 3.36(vs), 3.50(vs),6.95(s), 7.23(s),7.40(m), 8.70(m),9.04(vs). Extraction of this powder with boiling cyclohexane gave triphenylphosphine oxide (0.17 g., 0.6 mmole), white needles, m.p. 150-157°. Evaporation of the ether gave more triphenylphosphine oxide (4.75 g., 17 mmoles).

Reaction of α-Chlorocyclohexanone with Triphenylphosphine:

A. In acetonitrile:

α-Chlorocyclohexanone (2.00 g., 15 mmoles) and triphenylphosphine (4.15 g., 15.8 mmoles) were refluxed in 70 ml. of acetonitrile for 41 hrs. TLC (solvent A) indicated that only starting materials were present.

B. In Benzene:

To a solution of triphenylphosphine (4.15 g., 15.8 mmoles) and triethylamine (.354 g., 35 mmoles) in 65 ml. of benzene was added a solution of α-chlorocyclohexanone (2.00 g., 15 mmoles) in 20 ml. of benzene. Refluxed for 47 hrs. TLC (solvents A,B and E) gave spots only for the starting materials.

C. In Hexamethylphosphoric triamide:

A mixture of α- chlorocyclohexanone (7.00 g., 53 mmoles) and triphenylphosphine (15.9 g., 61 mmoles) was dissolved in 50ml. anhydrous hexamethylphosphoric triamide (distilled from calcium hydride). The colorless reaction solution was immersed in an oil bath preheated to 180°. After 12 minutes of heating, the solution rapidly turned yellow and then underwent a series of color changes which ended with a deep reddish purple. Heated at 180° for 5 hrs. TLC (solvent A) revealed the presence of unreacted starting materials and indicated that no cyclohexanone had been formed.

The solution was distilled to yield a colorless liquid, b.p. 85-86°/0.85 mm. v.p.c. on a glass 5% SE-30 column gave peaks only for α-chlorocyclohexanone and hexamethylphosphoric triamide. The distillation residue was a very viscous dark brown oil which solidified on standing. Benzene was added and the insoluble viscous semi-solid was dissolved in chloroform. The addition of ethyl acetate to the chloroform solution precipitated a tan solid which, however, rapidly changed to a purple oil when an attempt was made to collect it. If other products were formed, none could be isolated as pure substances.

Reaction of α-Bromocyclohexanone with Triphenylphosphine:

A. In diethylmalonate-acetonitrile at 25°:

Triphenylphosphine (7.40 g., 28.3 mmoles) was dissolved in diethylmalonate (25 ml. or 26.4 g., 0.165 mole) at room temperature. A solution of α-bromocyclohexanone (5.00 g., 28.3 mmoles) in 10 ml. acetonitrile was added dropwise during 60 min. After several minutes of addition, the clear solution abruptly became faintly cloudy. As the addition continued, the cloudiness gradually disappeared and the solution remained clear and colorless during the remaining

7.5 hours.of stirring.

The solution was distilled to dryness using a vacuum pump. The colorless distillate, 29.35 g., was analyzed by v.p.c. on a 5' x 1/4" glass column of silicone gum rubber 5% SE-30 on 60/80 DMCS Chromasorb W at 129°. It was found that in addition to diethylmalonate, the distillate contained α-bromocyclohexanone (1.61 g., 9.1 mmoles, 32% recovery) and cyclohexanone (0.81 g., 8.27 mmoles, 29% yield). The peak areas were compared to calibration lines obtained by injection of equally dilute solutions of known concentration in each of the components on the same column under identical conditions.

The brown distillation residue was triturated with benzene. The insoluble brown lumpy solid, 4.98 g., gave on TLC (solvents A and D) 6 spots and from it no pure substances were obtained. The benzene solution by TLC (solvent D) contained only triphenylphosphine and triphenylphosphine oxide. Excess methyl iodide was added and the crystalline, insoluble methyltriphenylphosphonium iodide (3.10g., m.p.179-182°) was collected. This corresponds to a recovery of

2.0 g., 7.64 mmoles, (27%) of triphenylphosphine. Evaporation of the benzene left triphenylphosphine oxide (1.50 g., 5.4 mmoles, 19%), m.p. 145-153°, identified by IR ($CHCl_3$).

B. In Diethylmalonate at 120°:

A mixture of α-bromocyclohexanone (5.01 g., 28.3 mmoles) and triphenylphosphine (7.42 g., 28.3 mmoles) was heated at 115-120° in 28 ml. of diethylmalonate for 1.5 hrs. The initially light yellow-green solution underwent a series of color changes and within 9 minutes a brown insoluble solid had formed and the solution had turned a deep red-brown.

The attempt to collect the purple insoluble material was not successful as it rapidly changed to a purple oil in a Buchner funnel. The solution was distilled to dryness using a vacuum pump to yield 27.22 g. of colorless distillate. Injected on a 5' x 1/4" glass column of 5% SE-30 at 129°. In addition to diethylmalonate, two other clearly defined peaks were obtained at lower retention times. The first of these was due to cyclohexanone (0.68 g., 6.94 mmoles, 24%) but the second peak, of approximately equal area, could not be assigned. No unreacted α-bromocyclohexanone was detected by v.p.c.

It is unlikely that the unidentified material is 2-cyclohexenone, because a UV spectrum (EtOH) of the distillate showed only strong tail-end absorption and faint absorption in the region 260-280 mμ.

The distillation residue, a dark viscous semi-solid, gave at least six spots by TLC (solvent D). Its NMR spectrum ($CDCl_3$) showed a complex multiplet 7.2-8.0 δ (aromatic H's) and small signals due to diethylmalonate protons.

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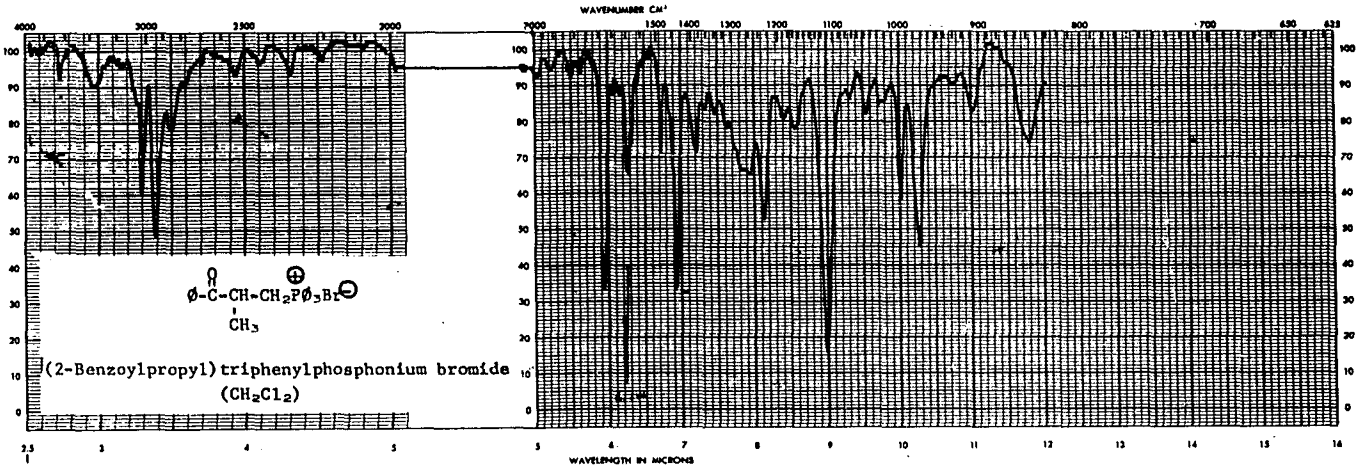
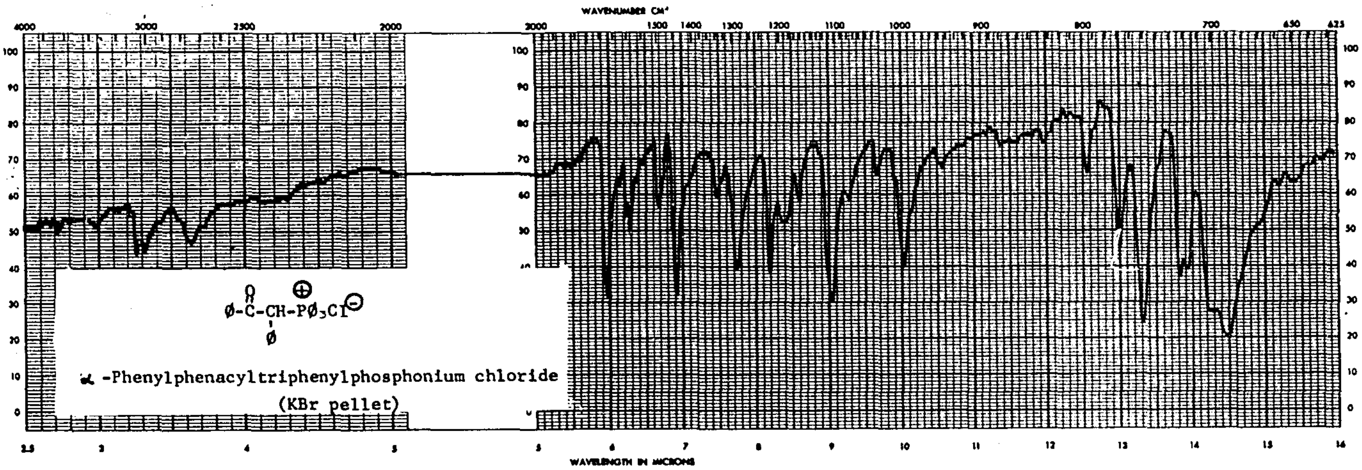


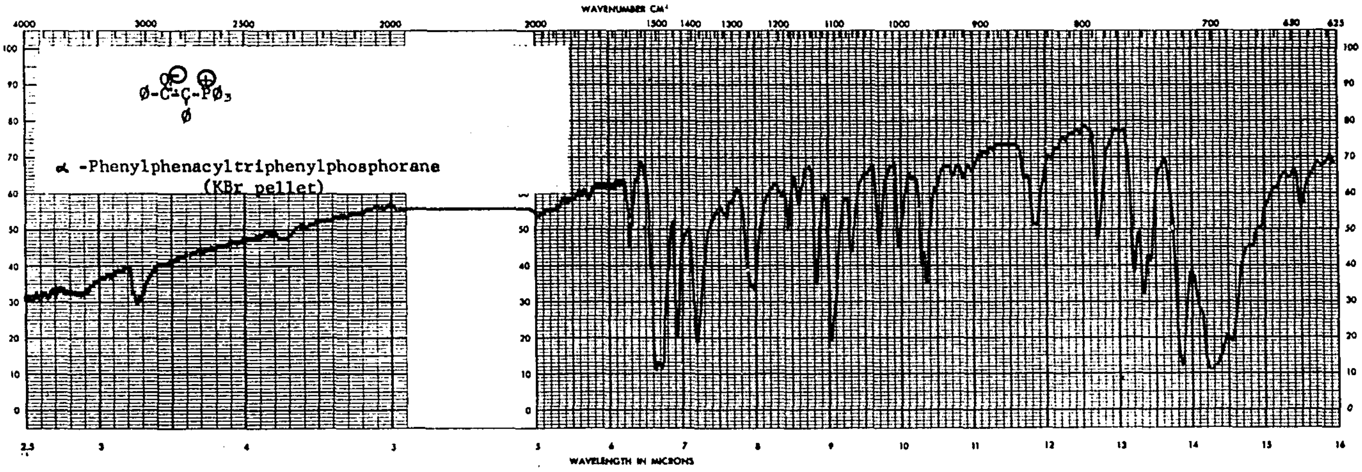
$\phi\text{-}\overset{O}{\overset{\|}{C}}\text{-}\underset{CH_3}{CH}\text{-}CH_2\overset{\oplus}{P}\phi_3Br^{\ominus}$

(2-Benzoylpropyl)triphenylphosphonium bromide
(CH_2Cl_2)



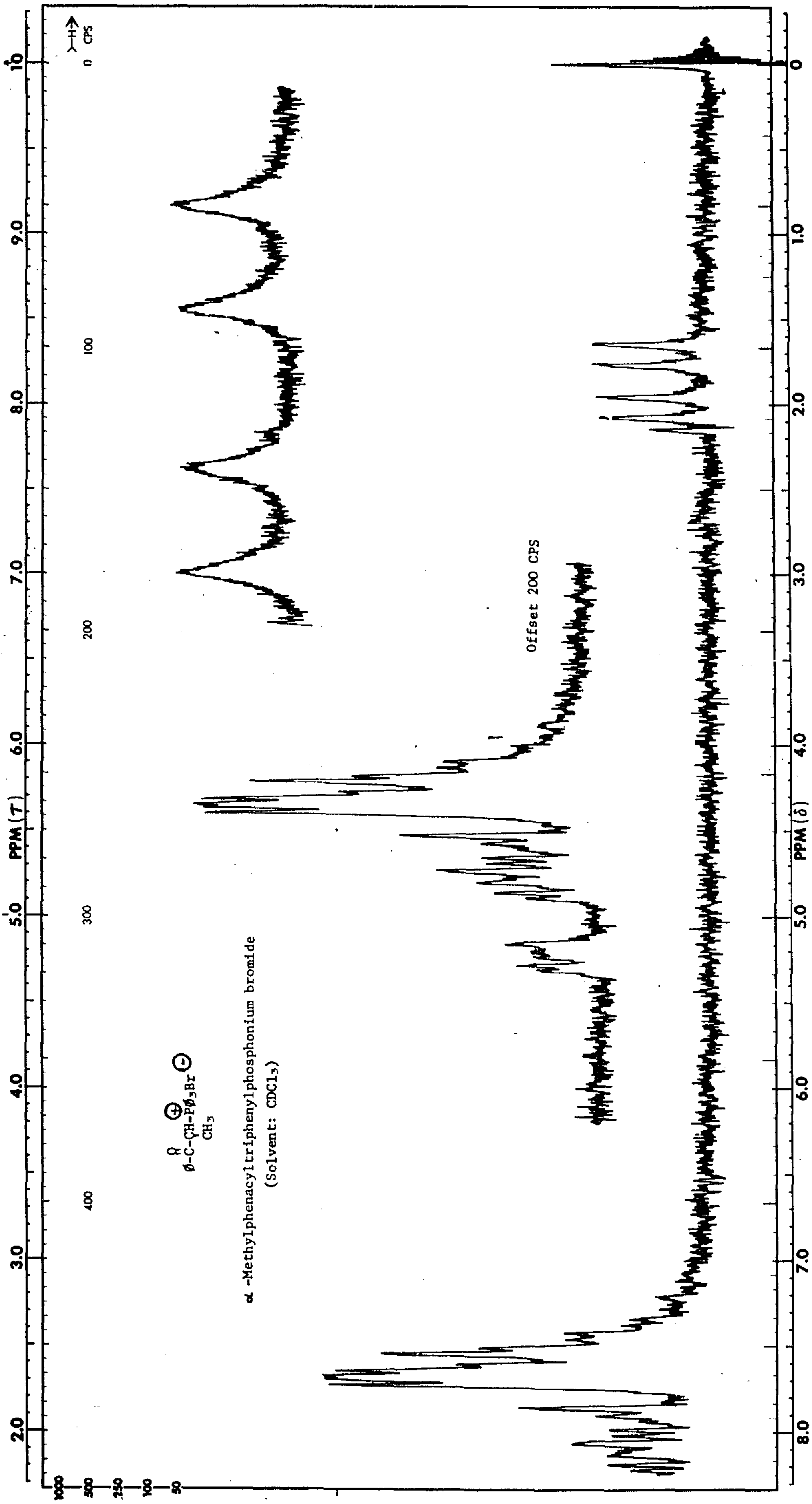
$\phi\text{-}\overset{O}{\overset{\|}{C}}\text{-}\underset{\phi}{CH}\text{-}\overset{\oplus}{P}\phi_3Cl^{\ominus}$

α -Phenylphenacyltriphenylphosphonium chloride
(KBr pellet)



$\phi\text{-}\overset{O^{\ominus}}{C}\text{=}\underset{\phi}{C}\text{-}\overset{\oplus}{P}\phi_3$

α -Phenylphenacyltriphenylphosphorane
(KBr pellet)



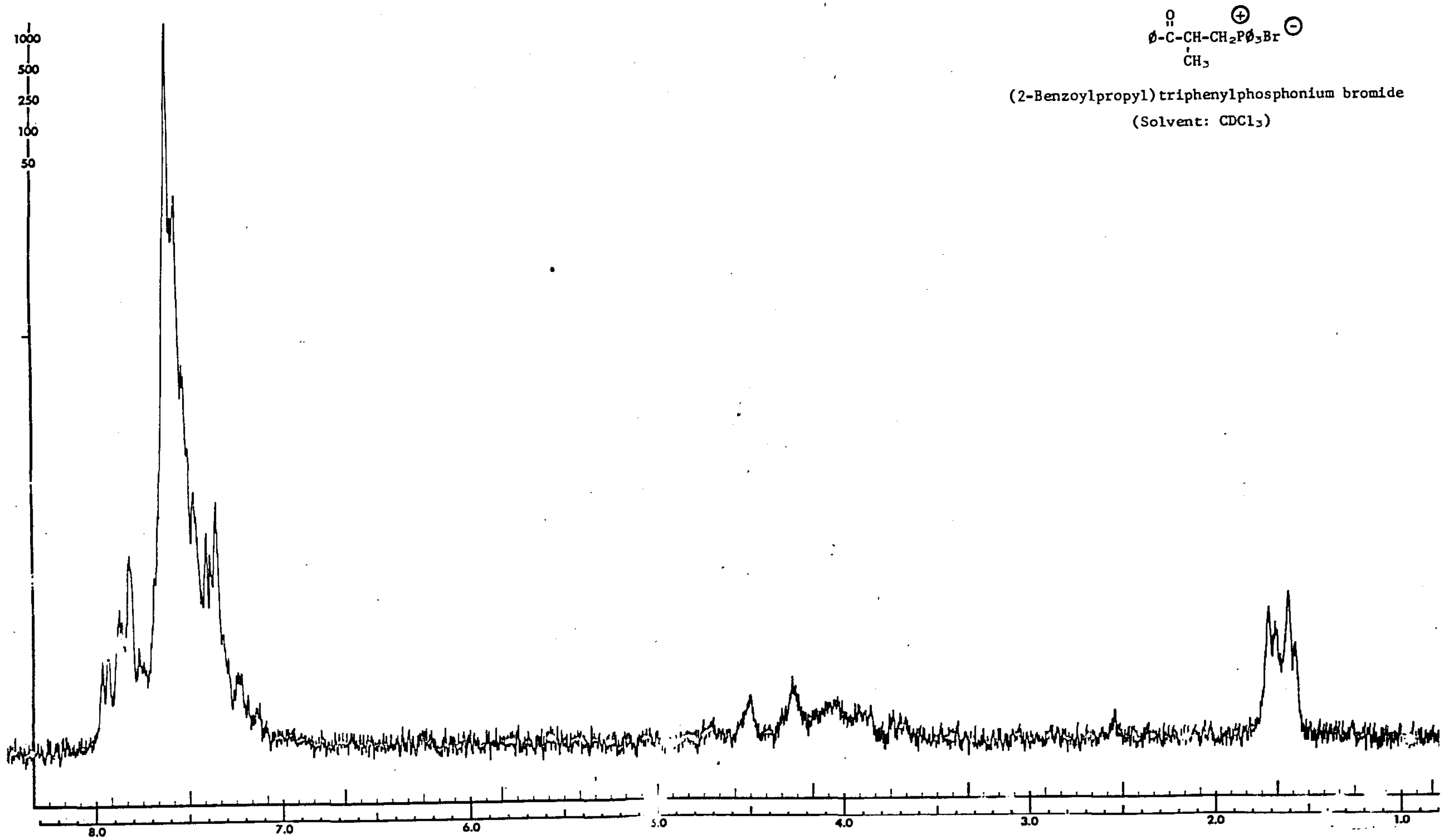
α-Methylphenacyltriphenylphosphonium bromide

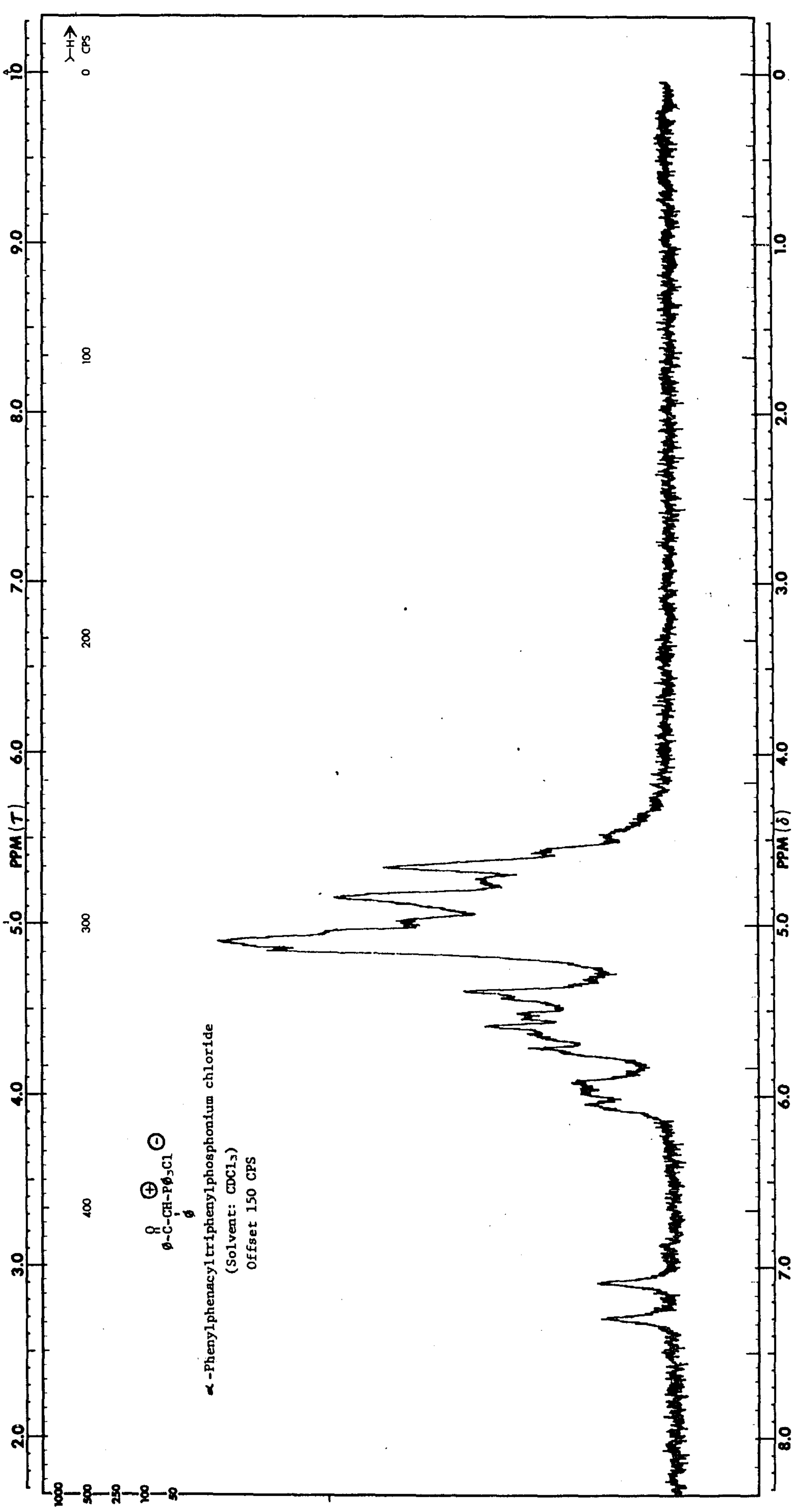
(Solvent: CDCl₃)

$$\phi\text{-}\overset{O}{\overset{\|}{C}}\text{-}\underset{CH_3}{CH}\text{-}CH_2\overset{\oplus}{P}\phi_3Br^{\ominus}$$

(2-Benzoylpropyl)triphenylphosphonium bromide

(Solvent: CDCl$_3$)




α-Phenylphenacyltriphenylphosphonium chloride
(Solvent: CDCl3)
Offset 150 CPS
ø-C(=O)-CH(ø)-P⊕ø3Cl⊖
PPM (τ)
10
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
>-H→
0 CPS
100
200
300
400
PPM (δ)
0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
1000
500
250
100
50

VITA

Mr. Rein Virkhaus was born on September 24, 1938, in Tartu, Estonia. He attended Harvard College and received his Bachelor of Arts degree in 1959, having majored in Chemistry. After a brief tour of duty in the United States Army, he entered Lehigh University in the fall of 1960 to undertake studies leading to the Doctor of Philosophy degree.

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