Organophosphorus Chemistry. III. The Reactions of Triphenylphosphine with Secondary α-Bromo Ketones and with 2-Bromodimedone

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α-Bromopropiophenone, 2-bromodimedone, and 2-bromocyclohexanone are dehalogenated with triphenylphosphine in methanol-containing solvents. In aprotic solution bromopropiophenone gives the α-ketophosphonium bromide. Bromodimedone gives 5,5-dimethyl-3-bromocyclohex-2-enone which is derived from the enol phosphonium bromide. Bromocyclohexanone gives a mixture of α- and β-ketophosphonium bromides and possibly the enol phosphonium bromide as well as a fuming solid which is probably triphenylphosphine dibromide. Most of the reactions, with the exception of the formation of the β-ketophosphonium salt, can be rationalized as proceeding by initial attack on bromine. The dehydrobromination leading to the β-keto salt is related to other eliminations involving the hindered bromoisobutyrophenone system.

It is known that primary α-bromo ketones such as bromoacetophenone **1** react with triphenylphosphine in aprotic solvents to give α-ketophosphonium bromides.[2] If **1** and triphenylphosphine are allowed to react in the presence of prototropic solvents such as methanol, then debromination occurs to give acetophenone.[2b] It is now known that debromination with triphenylphosphine in the initial presence of prototropic species occurs with many other "positive" halogen compounds including secondary and tertiary α-bromo ketones such as desyl bromide,[3,4] 2-bromocyclohexanone,[3-5] α-bromoisobutyrophenone,[6] and 2-methyl-2-bromocyclohexanone.[3]

We and others[2b-5] have postulated that the debrominations proceed by nucleophilic displacement on bromine by triphenylphosphine to give enolate bromophosphonium ion pairs. Reaction of such ion pairs with prototropic species then leads to the observed products: debrominatied ketone, triphenylphosphine oxide, and alkyl bromide (or hydrogen bromide). In the absence of prototropic species, these ion pairs interact to give either keto or enol triphenylphosphonium bromides.[7]

It has therefore been of interest to determine the nature of the products from the reactions of secondary and tertiary α-bromo ketones with triphenylphosphine in aprotic solvents. In this paper we report the reactions of triphenylphosphine with α-bromopropiophenone and with 2-bromodimedone as well as the current results of a reinvestigation of the 2-bromocyclohexanone–triphenylphosphine reaction system.

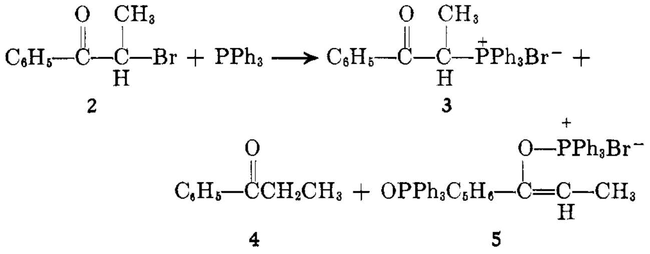
The reactions of α-bromopropiophenone **2** with triphenylphosphine parallel those of **1** although they are much slower in benzene or in more polar solvents. Treatment of **2** with triphenylphosphine in boiling benzene gives only 24% of α-methylphenacyltriphenylphosphonium bromide **3** after 1.5 hr.[8] After 31 hr a yield of 82.5% of **3** is obtained. As in the reactions of **1** small yields of dehalogenated ketone and triphenylphosphine oxide accompany the major yield of ketophosphonium salt.[2b] Reaction in acetonitrile at reflux for 31 hr also gives **3** (81%)[6] (Table I). Treatment of **2** with triphenylphosphine in benzene–methanol gives propiophenone **4** (94%) in 1.5 hr.

TABLE I

THE REACTIONS OF α-BROMOPROPIOPHENONE (2) WITH TRIPHENYLPHOSPHINE

Reaction conditions[a] (at reflux)	Time, hr	Yields, % 2	Ketophosphonium bromide	Propiophenone	Triphenylphosphine oxide
Dry benzene	1.5		24		
Dry benzene	31	9	82.5	13[b]	22
Benzene–methanol (8.4:1)	1.5	4	0	94[c]	65
Diethyl malonate	30		67	23[c]	34
Dry acetonitrile	31		81	11,[b] 14[d]	20

[a] All reactions done with a 1:1 bromo ketone–Ph_3P mole ratio. [b] As the 2,4-DNP. [c] From vpc on distillate after removal of triphenylphosphine oxide. [d] By nmr.



$$C_6H_5-\overset{\overset{O}{\|}}{C}-\underset{H}{\overset{\overset{CH_3}{|}}{C}}-Br + PPh_3 \longrightarrow C_6H_5-\overset{\overset{O}{\|}}{C}-\underset{H}{\overset{\overset{CH_3}{|}}{C}}-\overset{+}{P}Ph_3Br^- +$$

2 3

$$C_6H_5-\overset{\overset{O}{\|}}{C}CH_2CH_3 + OPPh_3C_5H_6-\overset{\overset{O-\overset{+}{P}Ph_3Br^-}{|}}{C}=\underset{H}{C}-CH_3$$

4 5

The dehalogenation of **2** is thus much more rapid than its conversion to **3** in benzene or even in acetonitrile.[9] The small yields of propiophenone and triphenylphosphine oxide obtained in the benzene and acetonitrile reactions could arise from the hydrolysis of an enol phosphonium salt **5** which is formed along with the major yield of **3**. We could not demonstrate the presence of any **5** at least in the benzene reaction

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[2] (a) F. Ramirez and S. Dershowitz, *J. Org. Chem.*, **22**, 41 (1957); (b) I. J. Borowitz and R. Virkhaus, *J. Am. Chem. Soc.*, **85**, 2183 (1963).

[3] I. J. Borowitz and L. I. Grossman, *Tetrahedron Letters*, **No. 11**, 471 (1962).

[4] (a) H. Hoffmann and H. J. Diehr, *ibid.*, **No. 13**, 583 (1962); (b) S. Trippett, *J. Chem. Soc.*, 2337 (1962).

[5] P. A. Chopard, R. F. Hudson, and G. Klopman, *ibid.*, 1379 (1965).

[6] R. Virkhaus, Ph.D. Dissertation, Lehigh University, 1965.

[7] The possibility that nucleophilic attack on bromine by triphenylphosphine occurs only in the presence of hydroxylic species must also be considered. In this event ketophosphonium salt formation in aprotic media could occur by direct displacement of bromide ion while enol phosphonium salts might be formed *via* several possibilities. Our current kinetic and other studies relating to these various possibilities are continuing and will be published in subsequent papers.

[8] Bromoacetophenone gives 79–85% phenacyltriphenylphosphonium bromide in 1.5 hr under these conditions (*cf.* ref 2b).

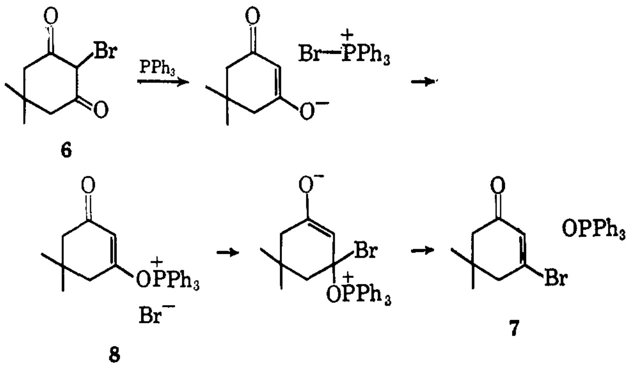
[9] The rate of reaction in acetonitrile is probably greater than in the less polar solvent benzene in these reactions. The acceleration of reaction in the presence of alcohol, which leads to dehalogenation, most likely indicates that the alcohol, possibly by means of hydrogen bonding on carbonyl oxygen, makes attack on bromine more feasible; *i.e.* a concerted reaction involving immediate protonation of an incipient carbanion can prevail instead of the formation of an ion pair which involves charge separation.

(as followed by nmr). It is more likely that **4** arises from the initial presence of some moisture which causes dehalogenation as does added methanol. All of these reactions are run in anhydrous solvents under nitrogen, however, and it is also possible that there may remain unreacted bromo ketone which is dehalogenated during work-up by moisture and remaining triphenylphosphine.

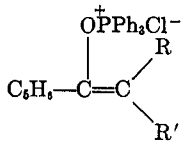
Treatment of **2** with triphenylphosphine in diethyl malonate results in a 16% decrease in phosphonium salt formation as compared with reaction in benzene (Table I) and a small increase (*ca.* 10%) in dehalogenated ketone. Contrary to our earlier observation[2b] we now find that the decrease in triphenylphosphonium salt formation from bromoacetophenone is similarly small (*ca.* 5% decrease from a reaction at room temperature, 20% decrease from a reaction at 125°, compared to a yield of 79–85% in benzene or acetonitrile).[6] We had previously suggested that the decrease in phosphonium salt formation was due to proton transfer by the malonate to our postulated enolate bromophosphonium ion pair.[2b] We do not now assign particular significance to the actually small decrease in phosphonium salt formation which occurs in diethyl malonate. The previously reported large decrease in phosphonium salt yield may have been due to traces of moisture or ethanol in the diethyl malonate.[10a]

The ketophosphonium salt **3** was shown to be stable to boiling methanol as had been previously demonstrated for phenacyltriphenylphosphonium bromide.[3] The structure proof of **3** is given in the Experimental Section.

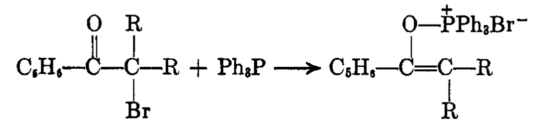
The reaction of 2-bromodimedone **6** with triphenylphosphine in boiling benzene gives 5,5-dimethyl-3-bromocyclohexenone **7** (29%) and triphenylphosphine oxide but no ketophosphonium bromide.[3] Reaction in boiling cyclohexane allows a better work-up and affords **7** (81%) and triphenylphosphine oxide (85%). Formation of **7** occurs presumably *via* the formation of the enol phosphonium bromide **8** which then undergoes Michael addition of bromide ion and subsequent loss of triphenylphosphine oxide.[10b]



Our original isolation of **7** afforded some of the first evidence for the intermediacy of an enol phosphonium bromide in the reaction of at least some bromo ketones with triphenylphosphine. It is recognized that **6**, a 2-bromo 1,3-diketone, is a special case which allows formation of an especially stable enol phosphonium bromide. Since our original communication Speziale and Partos[11] have isolated stable enol triphenylphosphonium salts **9–11** from chlorodiphenylacetophenone, dichlorophenylacetophenone, and trichloroacetophenone, respectively. Treatment of bromodiphenylacetophenone with triphenylphosphine gives the isolable enol phosphonium bromide **12** (80%).[12] In all of these cases it is likely that triphenylphosphine attacks the halogen to give an enolate halophosphonium ion pair. Attack on bromine and even chlorine is facilitated by the additional electron-withdrawing groups (carbonyl, phenyl, or chlorine) which additionally stabilize the resultant enolate. The ion pair interacts to form an enol phosphonium salt rather than a ketophosphonium salt. The preference for O rather than C phosphorylation of the enolate may be due to several factors. In the cases leading to **9–12** a steric factor should favor the less crowded oxygen site. In these cases and the bromodimedone case as well C phosphorylation may also be due to reaction of bromotriphenylphosphonium cation with the site of relatively greater negative charge: oxygen.[13]



9, R = R′ = Ph
10, R = Ph; R′ = Cl
11, R = R′ = Cl



$$C_6H_5-\overset{O}{\overset{\|}{C}}-\underset{Br}{\overset{R}{C}}-R + Ph_3P \longrightarrow C_6H_5-\overset{O-\overset{+}{P}Ph_3Br^-}{C}=\underset{R}{C}-R$$

12, R = Ph

The conversion of **8** to **7** at 80° is paralleled by the reported pyrolyses of **9** and **10** to give triphenylethylene and dichlorostilbene, respectively.[11] The structure of **7** follows from its correct elemental analysis and its conversion to dimedone (isolated as the formaldehyde derivative) with aqueous alcoholic sodium hydroxide. The infrared spectrum of **7** has carbonyl and double bond absorption at 1675 and 1605 cm^{-1}, respectively. Its ultraviolet spectrum exhibited λ_{max}^{EtOH} 245 mμ (ϵ 13,400) in reasonable agreement with a 3-bromocyclohexenone structure.[14] The nmr spectrum of **7** is in agreement with a 3-bromoenone structure (see the Experimental Section).

Treatment of **6** with triphenylphosphine in benzene–methanol gives dimedone (68%). The debromination can occur *via* either reaction with the postulated ion pair or by solvolysis of **8**.

2-Bromocyclohexanone **13** is debrominated with triphenylphosphine in boiling benzene–methanol to give cyclohexanone **14** (81%). It was found that, if the reagents were mixed in benzene and methanol was added after 1 hr followed by a reflux period of 23 hr,

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[10] (a) Further investigations bearing on the possible interception of enolate halophosphonium ion pairs will be reported elsewhere. (b) A referee has suggested that **7** arises *via* the intermediacy of the 1,3-diketo-2-triphenylphosphonium salt. Although this possibility deserves further thought we believe that the enol phosphonium salt **8** is more likely in this case.

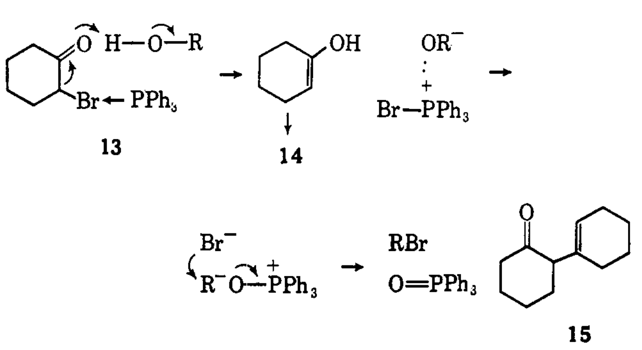
[11] (a) A. J. Speziale and R. D. Partos, *J. Am. Chem. Soc.*, **85**, 3312 (1963); (b) R. D. Partos and A. J. Speziale, *ibid.*, **87**, 5068 (1965).

[12] K. Kirby, research in progress.

[13] R. F. Hudson[5] has cited a correlation of frontier electron densities in an enolate anion with the site of phosphorylation.

[14] A. C. Nussbaum, O. Mancera, R. Daniels, G. Rosenkranz, and C. Djerassi, *J. Am. Chem. Soc.*, **73**, 3263 (1951).

cyclohexanone (88%) is again obtained. Since we find that reaction in dry benzene is not too rapid it is likely that methanol is present during the major part of reaction in this case (see ref 4b). The debromination of **13** in excess methanol to give **14** is related to our other observed dehalogenations and most likely proceeds *via* attack on bromine by triphenylphosphine.



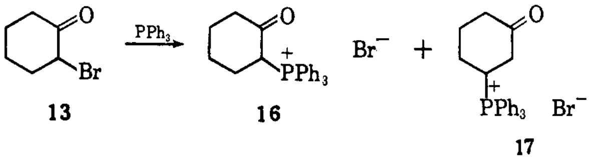
The reactions of **13** with triphenylphosphine in aprotic solvents are much more complex. Our early reactions in benzene or acetonitrile led to no isolable keto or enolphosphonium salts but varying amounts of triphenylphosphine oxide, its hydrobromide hydrate, and small yields of cyclohexanone.[6] The material balance in these reactions was poor however. Thus reaction of **13** with triphenylphosphine in dry acetonitrile gave about 17% of cyclohexanone (vpc on distillate from reaction mixture).[2b,6] The residue had infrared bands at 1705, 1625, and 1590 cm^{-1} and other bands which we now recognize as belonging to the 2- and 3-keto phosphonium salts (see below).

We had also previously reported that reaction of **13** with triphenylphosphine in the presence of excess diethyl malonate at 120° led to high yields of cyclohexanone **14**.[2b] Careful repetition of this work has given **14** in only 24% yield (vpc on distilled material).[6] A second vpc peak which was not **13** or cyclohexenone (different and longer retention time) was also found. Since Hudson[15] has now found that 2-cyclohexenylcyclohexanone **15** is formed in the reactions of **13** with triphenylphosphine with limiting amounts of alcohol, it is quite possible that our second vpc component was **15**. It is also possible that some cyclohexanone condenses to even more complex aldol derivatives under our conditions. Reaction of **13** with triphenylphosphine in diethyl malonate in acetonitrile at 25° gave **14** (29%) and none of the suspected **15**. In view of the complexity of the bromocyclohexanone reactions we will not now assign a special significance to these malonate results.

It was difficult to judge the extent of actual reaction prior to work-up in these early reactions.[16] The occurrence of small yields of **14** in these reactions may have been due to residual moisture in the solvent. The amount of triphenylphosphine left in such runs was at first qualitatively determined by tlc and in some runs by quaternization with methyl iodide. The latter method was too slow for a quantitative determination and gave a mixture of methyltriphenylphosphonium iodide and bromide which could be used as an approximate indication of the triphenylphosphine left. It was most meaningful, of course, for early stages of reaction when little bromide ion was present. More recently it was found that triphenylphosphine could be accurately determined by its rapid and quantitative precipitation with mercuric chloride to give the complex $HgCl_2 \cdot PPh_3$.[17] This technique and the more rigorous drying of solvents has now given us the following results.

Treatment of **13** with triphenylphosphine in boiling acetonitrile (0.28 *M* concentration) for 18 hr gives a low-melting mixture of the 2-ketophosphonium salt **16** (*ca.* 50%) and triphenylphosphine oxide (*ca.* 42%). Small amounts of **13** and **14** are also obtained.

We find that the reaction of **13** with triphenylphosphine in dry boiling benzene (2 M concentration) for 4 hr goes to completion and gives the 3-ketotriphenylphosphonium salt **17** as the only benzene-insoluble material. In more dilute benzene solution (0.11 *M*) the reaction is complete after 20 hr to give this salt (*ca.* 8%) and triphenylphosphine oxide (49%). The latter reaction conditions are related to many previous runs from which it was difficult to isolate products containing a cyclohexyl moiety. Only small amounts of cyclohexanone are present. In such runs we have at times isolated a white solid which rapidly fumes in moist air and changes to a red-brown oil and then a tan solid. The tan solid was triphenylphosphine oxide hydrobromide hydrate. The initial solid was probably triphenylphosphine dibromide Ph_3PBr_2 which behaves similarly upon exposure to moist air. This solid was sometimes the only benzene-insoluble material formed (instead of the ketophosphonium salts). It has been confirmed as to structure by Hudson.[15]



Reaction of **13** with triphenylphosphine in anhydrous diethyl ether gives an immediate precipitate of a small amount of solid which discolors and fumes in the air. It is probably triphenylphosphine dibromide as is formed in dilute benzene solution. Most of the triphenylphosphine is left unreacted (68% by quaternization with methyl iodide).

Finally, reaction of **13** with 1 equiv of triphenylphosphine (no solvent) at 85° gives both of the ketophosphonium salts **16** and **17** (55% crude yield, purified to 35%).

Our data indicate that both the 2- and 3-ketocyclohexylphosphonium salts are formed in the neat reaction with the 2-keto isomer **16** probably predominating. Thus treatment of the two main fractions of ketophosphonium salts from the above run with 1 *N* sodium hydroxide gave (1) the keto ylid **18** and mainly triphenylphosphine; (2) keto ylid only (triphenylphosphine by tlc). Since the keto ylid[18] is derived only from the 2-ketophosphonium salt while triphenyl-

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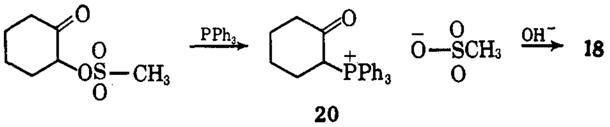
[15] We are indebted to Dr. R. F. Hudson for his manuscript prior to publication.

[16] We did not have availability of nmr for our early work whereby disappearance of **13** can be noted.

[17] F. A. Cotton and G. Wilkinson, "Advanced Inorganic Chemistry," Interscience Publishers, Inc., New York, N. Y., 1962, p 488.

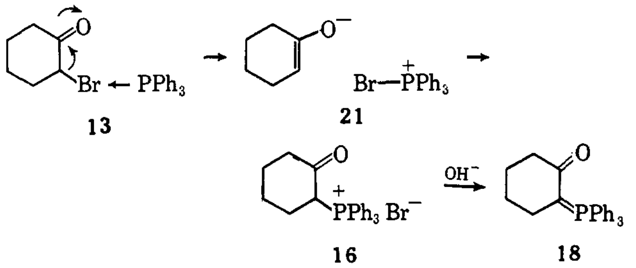
[18] H. O. House and H. Babad, *J. Org. Chem.*, **28**, 90 (1963). We are indebted to Professor House for a genuine sample of **18**.

phosphine results from a β elimination of the 3-ketophosphonium salt,[5] the salt fractions are (1) 1:9 **16**:**17** and (2) all **16** or about 18% **16** and 11% **17**. These yields are minimal in view of the difficulties encountered in separating the salts from other compounds present and in analyzing the crude salt fractions. The infrared spectra of the various fractions are quite similar. They are also similar to the infrared spectrum of the 2-ketocyclohexylphosphonium mesylate **20** (it gives the keto ylid **18** in 76%) which is formed (49%) from 2-mesyloxycyclohexanone **19** and triphenylphosphine.[19] The stability of **16** and **17** to alcohol is demonstrated by their recrystallization from ethanol–ethyl acetate. No thermal decomposition of **16** to the keto ylid **18** was noted. We have not found any evidence for the presence of **18** in any of the reaction mixtures from **13** and triphenylphosphine.

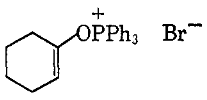


19 **20**

2-Ketocyclohexyltriphenylphosphonium bromide **16** may arise *via* interaction of the ion pair **21** formed by attack on bromine of **13** by triphenylphosphine. The possibility of its formation from the enol phosphonium bromide **22** has been suggested by Chopard and Hudson.[20]



We have tried to obtain evidence for the presence of **22** in the bromocyclohexanone reactions with little success. Since the yields of the ketophosphonium bromides seem to be about 55% at best it seemed reasonable that **22** might be a major product. Our evidence for **22** to date is sparse and includes the formation of a weak nmr multiplet centered at 352 cps (τ 4.15) in the reaction of **13** with triphenylphosphine in deuterioacetonitrile (as followed in a sealed nmr tube). This multiplet may be the vinyl proton of **22** since the ketophosphonium salts have no absorption in this region and diethyl cyclohexenyl phosphate **23** shows vinyl proton absorption in the nmr at 324 cps.[21] The 352-cps multiplet decreased only slightly after the addition of D_2O however.



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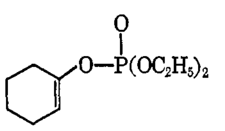
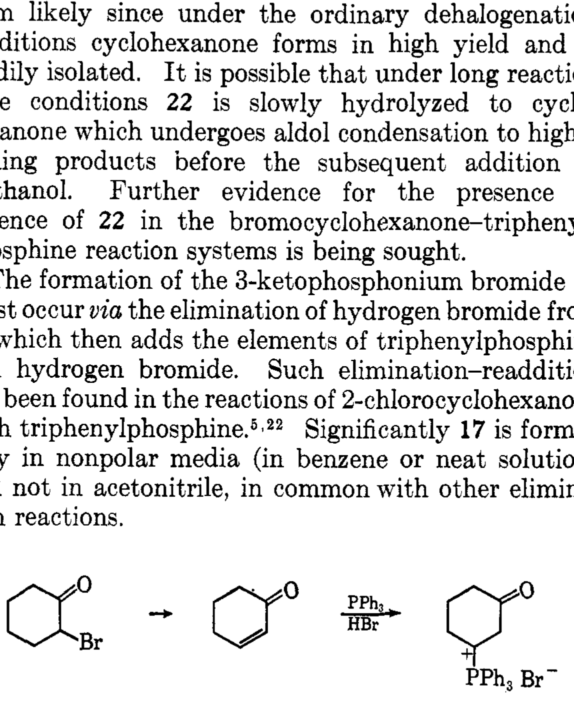


23

Solvolytic evidence for the presence of **22** has not been forthcoming. If **13** and triphenylphosphine are heated at reflux in benzene for 24 hr, the subsequent addition of excess methanol does not give any cyclohexanone. Thus either there is no appreciable amount of **22** at the time of methanol addition or cyclohexanone does form but reacts further. The latter possibility does not seem likely since under the ordinary dehalogenation conditions cyclohexanone forms in high yield and is readily isolated. It is possible that under long reaction time conditions **22** is slowly hydrolyzed to cyclohexanone which undergoes aldol condensation to higher boiling products before the subsequent addition of methanol. Further evidence for the presence or absence of **22** in the bromocyclohexanone–triphenylphosphine reaction systems is being sought.

The formation of the 3-ketophosphonium bromide **17** must occur *via* the elimination of hydrogen bromide from **13** which then adds the elements of triphenylphosphine and hydrogen bromide. Such elimination–readdition has been found in the reactions of 2-chlorocyclohexanone with triphenylphosphine.[5,22] Significantly **17** is formed only in nonpolar media (in benzene or neat solution) and not in acetonitrile, in common with other elimination reactions.



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The elimination of hydrogen bromide from **13** competes effectively with attack on bromine by triphenylphosphine since the bromide of **13** is predominantly axial and hindered. Displacement of bromide ion by an SN2 mechanism, at least a formal possibility in the formation of α-ketophosphonium salts, is especially hindered in the cyclohexyl system. Since the bromine of bromopropiophenone **2** is less hindered, displacement on bromine occurs to the exclusion of β elimination to give an ion pair which interacts to give the α-ketophosphonium bromide **3**.

The concept of hindered halo ketones giving β elimination when possible upon reaction with triphenylphosphine is further advanced by our observations on the reactions of α-bromoisobutyrophenone **24**.[6,12] This bromo ketone is debrominated to isobutyrophenone **25** (97%) with triphenylphosphine and methanol when both are present in excess. Reaction of **24** with 1 equiv of triphenylphosphine and excess methanol gives methacrylophenone **26** (13%) as well as **25** (75%). More strikingly, reaction of **24** with triphenylphosphine in dry xylene or acetonitrile gives the β-ketophosphonium bromide **27** (48–56%) and no α-ketophosphonium salt. Thus β elimination occurs readily in aprotic systems and even somewhat in the presence of methanol. These reactions will be discussed in more detail in a subsequent paper.

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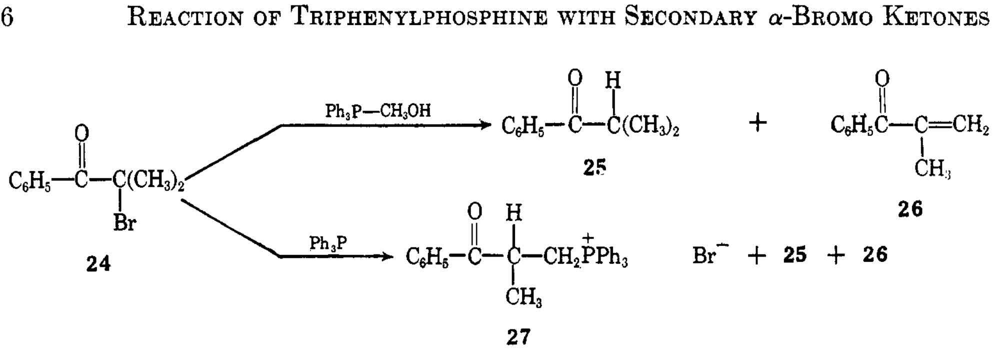
[19] P. Rusek, research in progress.

[20] P. A. Chopard and R. F. Hudson, *J. Chem. Soc.*, in press.

[21] The vinyl proton may be due to olefinic species other than **22** such as possibly **15**.

[22] The nature of the species causing the dehydrobromination is not known. It may be triphenylphosphine, a weak base, or the enolate derived by attack on bromocyclohexanone as suggested by Hudson.[20]



Experimental Section

Microanalyses were performed by Professor V. B. Fish of the Department of Chemistry, Lehigh University, and Galbraith Laboratories, Knoxville, Tenn. Infrared spectra were recorded on a Beckman IR-8 infrared spectrophotometer. Gas chromatograms were recorded on a Varian Aerograph A-700 chromatograph using various columns as indicated. Nmr spectra were recorded on a Varian A-60A spectrometer with TMS as an internal standard. Melting points were taken on a Mel-Temp apparatus. They as well as boiling points are uncorrected.

All of the solvents used were distilled from phosphorus pentoxide or calcium hydride. Thin layer chromatography plates were prepared with Brinkmann silica gel HF_{254} and were developed in solution of 5% ethyl acetate–benzene or 25% methanol–benzene (designated A or B, respectively). Triphenylphosphine was recrystallized from diethyl ether and dried under vacuum. All reactions involving triphenylphosphine were conducted under an atmosphere of dry nitrogen.

α-Bromopropiophenone was prepared by bromination of propiophenone in diethyl ether (75%).[23] It was distilled through a vacuum-jacketed, silvered, 22-cm Vigreaux column, bp 156–157.5° (42 mm). It was stored at 0–5°. *Anal.* Calcd for C_9H_9BrO: Br, 37.50. Found: Br, 37.71.

2-Bromodimedone was synthesized from dimedone in methanol with aqueous cupric bromide and potassium bromide.[24] It was obtained as a cream-colored solid, mp 169–170°, and recrystallized from 4:1 (v/v) methanol–water to give mp 174–176° (52%).

2-Bromocyclohexanone was prepared by bromination of cyclohexanone in water at 0–5°,[25] distilled from magnesium oxide, bp 54–56° (0.3 mm) (64%). It was stored at 0–5°.

The Reaction of Bromopropiophenone with Triphenylphosphine. A. In Benzene.—A mixture of bromopropiophenone (6.00 g, 0.0281 mole) and triphenylphosphine (7.42 g, 0.0283 mole) in benzene (60 ml) was heated at reflux for 1.5 hr to give insoluble α-methylphenacyltriphenylphosphonium bromide (**3**, 3.26 g, 0.00687 mole, 24%), mp 245–247° (from ethanol–water), lit.[26] mp 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. In a similar run heated at reflux for 31 hr, **3** (83%) was obtained. In runs of 10, 17, and 21 hr (same concentration) yields of 62, 73, and 78% of **3** were obtained. Reaction in more concentrated solution (0.84 *M*) gave **3** (83%) in about 2 hr. The infrared spectrum (KBr) of **3** exhibited peaks at 6.0 (s), 6.31 (m), 6.73 (m), 6.96 (s), 8.24 (s), 9.03 (s), 10.02 (m), and 10.43 ms) μ. The nmr spectrum ($CDCl_3$) of **3** exhibited peaks including two doublets centered at τ 7.96 and 8.27 ($J_{\mathrm{H,CH_3}} = 7.5$ cps for each; $J_{\mathrm{P^{31}H}} = 19$ cps) (C-methyl), multiplets at 1.19–1.50 and at 1.66–2.83 (aromatic protons); peak areas in the ratio of 2.6:20.

B. In Benzene–Methanol.—Bromopropiophenone (1.62 g, 0.0076 mole) and triphenylphosphine (2.00 g, 0.0076 mole) in methanol (3 ml)–benzene (25 ml) were refluxed for 1.5 hr. No triphenylphosphine was left as shown by no reaction of an aliquot with mercuric chloride in acetone. After removal of solvents and boiling with cyclohexane triphenylphosphine oxide (1.347 g, 0.005 mole, 65%, mp 147–153°) was obtained. Removal of the solvent left 1.03 g of liquid which was 92:8 propiophenone 4–bromopropiophenone 2 (by nmr). This corresponds to yields of 0.96 g (94%) of **4** and 0.07 g (4%) of unreacted **2**.

C. In Benzene–Diethyl Malonate.—To triphenylphosphine (3.71 g, 0.0142 mole) in dry benzene (16 ml)–diethyl malonate (10 ml, 0.066 mole; pure by vpc) was added bromopropiophenone (3.00 g, 0.0140 mole) in benzene (6 ml). The mixture was heated at 85° (oil bath temperature) for 30 hr, and the resultant brown powder was collected and washed with benzene to give **3** (4.45 g, 0.0094 mole, 67%), mp 233–240° dec; the infrared spectrum was identical with genuine **3**. The residual solution was distilled to give a fraction of bp 45–47° (0.4 mm), 11.0 g; vpc (on 20% Carbowax 20 M on HMDS Chromosorb P, column temperature 142°, 100 ml/min) showed 4% **4** or *ca.* 0.44 g, 0.0033 mole, 25%.

D. In Acetonitrile.—A mixture of **2** (6.00 g, 0.0281 mole) and triphenylphosphine (7.42 g, 0.0283 mole) was heated at reflux in acetonitrile (70 ml) for 31 hr to give **3** (8.58 g, mp 241.5–246.5°). Distillation of the solvent and addition of benzene to the oily residue gave more **3** (2.22 g, total yield 10.8 g, 0.0228 mole, 81%). Tlc (solvent A) on the benzene solution showed **2**, **4**, and triphenylphosphine oxide. After reduction in volume the benzene solution was chromatographed on neutral aluminum oxide (60 g on a column 2 cm in diameter) to give 0.60 g of liquid which was 88:12 of **4** to **2** (by nmr, 0.53 g, 14% **4**; 0.07 g, *ca.* 1% **2**); triphenylphosphine oxide [1.62 g, 0.00582 mole, 20%; infrared ($CHCl_3$) identical with a genuine sample].

Stability of 3 to Methanol.—The salt **3** (0.20 g) in methanol (10 ml) was refluxed for 30 hr. Tlc (1:1 ethyl acetate–methanol) showed only a spot for **3**; recovery of **3** was 0.196 g or 98%, mp and mmp 240–243°.

The Reaction of 2-Bromodimedone with Triphenylphosphine. A. In Benzene.—A mixture of 2-bromodimedone (**6**, 2.100 g, 0.0096 mole) and triphenylphosphine (2.59 g, 0.0099 mole) in benzene (25 ml) was refluxed for 2 days. Tlc (solvent A) showed two spots at R_f 0.0 and 0.5. Upon concentration of the mixture crude triphenylphosphine oxide (2.65 g) precipitated. Since it contained adsorbed enone (by infrared) it was recrystallized from cyclohexane and the supernatant liquid was added to the reaction mixture. After removal of solvent the residual oil was distilled from an oil-jacketed flask at 2.5 mm to give **7** (0.505 g, 26%). In a similar run involving partial removal of triphenylphosphine oxide (insoluble in ether) followed by distillation from an oil-jacketed flask at bath temperature 80–110° (0.1 mm), **7** was obtained in 29% yield. It was difficult to separate **7** in better yield.

B. In Cyclohexane.—A mixture of **6** (2.185 g, 0.010 mole) and triphenylphosphine (2.580 g, 0.0099 mole[27]) in cyclohexane (25 ml, freshly distilled from "Dri-Na") was refluxed for 14 hr; reaction complete (tlc). Upon cooling, triphenylphosphine oxide (2.326 g, 0.00836 mole, 85%, mp 151–155°) was obtained. The residual solvent was distilled through a silvered Vigreux column and the remaining oil was distilled from an oil-jacketed flask (bath temperature 80–110° at 0.1 mm) to give **7** (1.650 g, 0.0081 mole, 82%; one component by tlc and vpc).

5,5-Dimethyl-3-bromocyclohex-2-enone (**7**) exhibited infrared (CCl_4) bands at 1675 (carbonyl) and 1605 cm^{-1} (double bond); ultraviolet $\lambda_{\max}^{\mathrm{EtOH}}$ 245 mμ (ε 13,400); and nmr (CCl_4) peaks at τ 3.72 (olefinic triplet, J = 1 cps), 7.33 (doublet of C_4 H, J = 1 cps), 7.82 (singlet of C_6 H), and 8.93 (singlet, methyl H) with peak area ratios of 1:2:2:6. *Anal.* Calcd for $C_8H_{11}BrO$: C, 47.42; H, 5.46. Found: C, 47.41; H, 5.28. The slight splitting of C_2 and C_4 protons is due to allylic long-range effects.

To **7** (0.130 g, 0.00064 mole) in 95% ethanol (2–3 ml) was added 10% sodium hydroxide (1 ml, *ca.* 0.0025 mole). The mixture was warmed at 70–90° (bath temperature) for 1 hr. The ultraviolet spectrum of the resulting mixture had $\lambda_{\max}^{\mathrm{EtOH}}$ 282 mμ [the anion of dimedone has $\lambda_{\max}^{\mathrm{EtOH}}$ 280 mμ (ε 2000)[28]]. The mixture was adjusted to pH 7 and *ca.* 50% aqueous alcohol

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[27] An excess of triphenylphosphine was purposely avoided so as to facilitate work-up.

[28] Confirmed by us on a genuine sample of dimedone.

composition. Formaldehyde (0.5 ml of 40% aqueous solution) was added. An oil formed (at 5°) which had an identical infrared with a genuine sample of the formaldehyde derivative of dimedone **26** (see below). Part of the oil solidified to give mp 186–189°, mmp 186–189° with genuine **26** (mp 186–188.5°).

C. In Methanol–Benzene.—A mixture of **6** (1.404 g, 0.0064 mole) and triphenylphosphine (1.847 g, 0.00706 mole) in methanol (10 ml)–benzene (40 ml) was refluxed for 2.5 days. After removal of solvents, methyl triphenylphosphonium bromide (0.224 g, 0.00063 mole, 9% from triphenylphosphine) was obtained as the only benzene-insoluble material, mp 228–230°.[29] From the benzene solution triphenylphosphine oxide (0.70 g, 36%) was obtained. The remaining oily solid could not be further crystallized. It was dissolved in 50% ethanol; formaldehyde (0.7 ml of 40% aqueous solution; *ca.* 0.007 mole) was added to give the condensation product of formaldehyde with dimedone **26** as a white solid (0.622 g, 0.0021 mole, equivalent to a 68% yield of dimedone, mp 188–189.5°, lit.[30] mp 189°; $\lambda_{\max}^{\mathrm{EtOH}}$ 256 mμ as for dimedone itself).

The Reaction of 2-Bromocyclohexanone with Triphenylphosphine. A. In Methanol–Benzene.—A mixture of 2-bromocyclohexanone (0.43 g, 0.0024 mole) and triphenylphosphine (0.85 g, 0.0033 mole) was heated at reflux in methanol (4 ml)–benzene (15 ml) for 18 hr. After removal of solvents by distillation through a silvered Vigreux column, cyclohexane was added. Triphenylphosphine oxide (yields up to 96% were obtained in related reactions) was removed and the residual liquid was determined by vpc to contain cyclohexanone (0.191 g, 0.00194 mole, 81%). In another run cyclohexanone was distilled from the reaction mixture at bp 55–56° (25 mm) and in 62% yield. The 2,4-DNP was prepared and found to be identical with that of genuine cyclohexanone, mp 158.5–159°, mmp 158.5–160.5° with genuine DNP of mp 160–161.5°. Occasionally methyltriphenylphosphonium bromide, mp 226–229°, was obtained in *ca.* 10% yield.

B. In Benzene with Addition of Methanol after 1 Hr.—Reaction of **13** (1.11 g, 0.0063 mole) with triphenylphosphine (1.74 g, 0.0066 mole) at reflux in benzene (25 ml) for 1 hr followed by addition of absolute methanol (5 ml) and a reflux period of 23 hr with the above work-up gave cyclohexanone (0.54 g, 88%).

C. In Benzene with Addition of Methanol after 24 Hr.—A mixture of **13** (0.800 g, 0.0045 mole) and triphenylphosphine (1.273 g, 0.0048 mole) in dry benzene (25 ml) was refluxed for 24 hr. Tlc (in benzene) of the resultant solution showed spots for triphenylphosphine, and an unknown component which did not move, but no **13** or **14**. Methanol (5 ml) was added and the mixture was refluxed for 2 hr. Tlc showed no changes from the previous composition. Removal of the benzene, addition of cyclohexane, removal of resultant solid (mp 80–120°), and vpc on the resultant solution showed no cyclohexanone or other volatile components to be present.

D. In Diethyl Malonate–Acetonitrile at 25°.—Triphenylphosphine (7.40 g, 0.0283 mole) was dissolved in dry diethyl malonate (25 ml, 26.4 g, 0.165 mole). A solution of **13** (5.00 g, 0.0283 mole) was added dropwise during 60 min. After an additional 7.5 hr the solution was distilled *in vacuo* to give 29.35 g of liquid which contained **13** (1.61 g, 32% recovery) and **14** (0.81 g, 29%) (by vpc on 5% SE-30 at 129°). The brown distillation residue gave triphenylphosphine (27–31% based on the mixture of methyltriphenylphosphonium bromide and iodide (3.10 g, mp 179–182°, formed with methyl iodide) and triphenylphosphine oxide (1.50 g, 19%).

E. In Diethyl Malonate at 120°.—A mixture of **13** (5.01 g, 0.0283 mole) and triphenylphosphine (7.42 g, 0.0283 mole) was heated at 115–120° in diethyl malonate (28 ml) for 1.5 hr. The solution colored rapidly and became red-brown in 9 min, depositing a brown solid. The solid was unstable and could not be collected. The solution was distilled *in vacuo* to give 27.22 g of liquid containing **14** (0.68 g, 24%) and a second unknown compound of *ca.* equal peak area (by vpc as above). The residue contained at least six components (tlc) and was not further investigated.

F. In Benzene (2 *M* Solution).—A mixture of **13** (8.78 g, 0.0495 mole) and triphenylphosphine (13.40 g, 0.0512 mole) was refluxed in benzene (25 ml) for 4 hr (no triphenylphosphine left) to give some semisolid in a clear solution. After numerous attempts at crystallization, a portion was solidified from ethyl acetate to give mp 203–206°; recrystallized to mp 212–213.5°. *Anal.* Calcd for $C_{24}H_{24}BrOP$: C, 65.61; H, 5.49; Br, 18.20; P, 7.07. Found: C, 65.53, 65.85; H, 5.76, 5.99; Br, 17.89; P, 6.82, 6.80.

G. In Benzene (0.12 *M* Solution).—A mixture of **13** (1.03 g, 0.0058 mole) and triphenylphosphine (1.52 g, 0.0058 mole) was refluxed in benzene (50 ml) for 20 hr (no triphenylphosphine left) to give only 0.21 g (8%) of the ketophosphonium salt(s) (identical infrared spectrum with that of known mixtures of **16** and **17**). The salt was only **17** in this case since it gave triphenylphosphine upon treatment with 10% aqueous sodium hydroxide (see below for further use of this method). Triphenylphosphine oxide was isolated in 49% yield (0.79 g). In a similar run (0.4 *M*) done previously on a 0.056-mole scale, 0.5 g of a white solid (triphenylphosphine dibromide) was isolated. It turned to an orange gum and then an orange solid while emitting white acidic fumes. The orange solid contained bromide ion (positive test with silver ion) and was a phosphonium salt (positive test with sodium tetraphenylboron). Upon treatment with 10% aqueous sodium hydroxide the orange solid gave triphenylphosphine oxide (ultraviolet and mixture melting point). The orange solid, mp 137.5–143°, was washed with ether (nothing found in the ether washings) to leave a solid, mp 137.5–143° (softens at 132.5°). It was found to be triphenylphosphine oxide hydrobromide hydrate. *Anal.* Calcd for $C_{18}H_{18}BrO_2P$: C, 57.46; H, 4.83; Br, 21.24; P, 8.23; mol wt, 376. Found: C, 57.16; H, 4.66; Br, 21.41; P, 8.36; mol wt, 363.

H. In Diethyl Ether.—A mixture of **13** (2.10 g, 0.0119 mole) and triphenylphosphine (3.12 g, 0.0119 mole) in dry ether (30 ml) gave an immediate white precipitate which was filtered under nitrogen. When exposed to the air it behaved similarly to the above-mentioned solid and became a brown gum (probably originally triphenylphosphine dibromide). Methyl iodide (10 ml) was added to the residual ether solution to give, after 5 hr, methyltriphenylphosphonium iodide–bromide (3.26 g, 68% if pure iodide). This corresponds to 68% of unreacted triphenylphosphine (71% if the salt were all bromide). Thus only a small part of **13** had reacted under the above conditions.

I. In Acetonitrile (0.28 *M* Solution).—A mixture of **13** (1.71 g, 0.0098 mole) and triphenylphosphine (2.55 g, 0.0098 mole) in acetonitrile (35 ml) was refluxed for 18 hr. No triphenylphosphine was left by mercuric chloride test. The solvent was distilled at 50° (0.4 mm) and contained small amounts of **13** and **14**. The residual oil (triphenylphosphine oxide and ketophosphonium salts by tlc and infrared) was crystallized from benzene–acetonitrile to give (1) 1.83 g of ketophosphonium salts, mp 105–120° (infrared that of **16** and **17**); (2) 0.68 g, *ca.* 1:1 ketophosphonium salts and triphenylphosphine oxide, mp 110–125°; and (3) 0.73 g of triphenylphosphine oxide, mp 142–148° (infrared identical with genuine sample). The yields are approximately 2.15 g of ketophosphonium salts (50%) and 1.07 g of triphenylphosphine oxide (42%).

In another run (0.38 *M*) a mixture of ketophosphonium salt and triphenylphosphine oxide (tlc) was formed. Upon treatment with 1 *N* aqueous sodium hydroxide a mixture of triphenylphosphine oxide (*ca.* 23%) and keto ylid **18** (*ca.* 9%, by nmr, infrared, and tlc) resulted. No triphenylphosphine was found. Thus all of the ketophosphonium salt in this reaction was 2-ketocyclohexyltriphenylphosphonium bromide (**16**).

J. In Acetonitrile (Followed by Nmr).—A mixture of **13** (0.28 g, 0.00156 mole) and triphenylphosphine (0.41 g, 0.00156 mole) in acetonitrile (0.79 g) under nitrogen in a tightly capped nmr tube was kept at room temperature for 4 hr (no change in nmr) and then warmed at 50°. The triplet (264, 272, and 277, cps) owing to the proton on C_2 (α-bromine carbon) of **13** slowly decreased and the aromatic protons changed from a singlet owing to triphenylphosphine, to a complex multiplet. A weak multiplet centered at 352 cps was noticed after 1 day and remained unchanged thereafter (slight decrease after addition of D_2O).

K. No Solvent.—A mixture of **13** (7.34 g, 0.0413 mole) and triphenylphosphine (10.80 g, 0.0413 mole) was gradually heated. At 50° all of the triphenylphosphine had dissolved. At 85° solid began to appear. After 45 min benzene (25 ml) was added and the mixture was heated at reflux for 1 hr to give 9.87 g of a benzene-insoluble semisolid, mp 110–160°; infrared ($CHCl_3$) was very similar to that of the purified ketophosphonium salt fractions (see below; 55% if pure ketophosphonium salts). Crystallization from ethyl acetate–methanol gave (1) 2.15 g, mp

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[29] G. Wittig and U. Schollkopf, *Ber.*, **87**, 1326 (1954).

[30] A. Vogel, "A Textbook of Practical Organic Chemistry," Longmans, Green and Co., London, 1951, p 332.

206–208°, **16** and **17**; (2) 2.95 g, mp 135–138°, **16**; (3) 1.17 g. The infrared spectra ($CHCl_3$) of all fractions were very similar and identical with that obtained in run F. They exhibited peaks at 2.95 (w), 3.4 (s), 3.6 (w), 4.1 (w), 5.85 (s), 6.15 (m), 6.28 (w), 6.72 (m), 6.92 (s), 7.25 (w), 7.95 (w), 8.05 (w), 8.15 (w), 8.8 (w), 9.0 (s), and 10.0 (m) μ. The peaks at 6.15 and 6.28 μ (1628 and 1590 cm^{-1}) varied in intensity in the different fractions. Fraction 1 (0.449 g) was dissolved in warm water and treated with 1 *N* sodium hydroxide to give an immediate precipitation of 0.305 g of a mixture of triphenylphosphine and the keto ylid **18**, mp 74–82° (identified by infrared and tlc). The mixture was shown to be *ca.* 1:9 keto ylid–triphenylphosphine as follows. An aliquot (0.125 g) was treated with mercuric chloride in acetone to give 0.185 g of $HgCl_2 \cdot (C_6H_5)_3P$, mp 301–305° dec. Therefore fraction 1 contained 89% 3-keto- and 11% of 2-ketocyclohexyltriphenylphosphonium bromide **17** and **16**. Fraction 2 (2.95 g, 0.0033 mole) was similarly treated with sodium hydroxide to give the keto ylid **18** only, 0.814 g (0.0023 mole, 70%), mp 237–239°, and no triphenylphosphine (tlc). Fraction 3 gave no precipitate with sodium hydroxide. These results correspond to minimum yields of 3.15 g of the 2-keto salt **16** (0.0072 mole, 18%) and 1.95 g of the 3-keto salt **17** (0.0044 mole, 11%). The keto ylid **18** was recrystallized twice from ethyl acetate to give mp 245–247°, mmp 228–238° with an impure genuine sample of **18** (mp 228–232°).[18] The conversion of **16** to keto ylid with sodium methoxide in methanol[26] gave much poorer yields. The keto ylid **18** exhibited diagnostic infrared peaks at 6.65 (s) and 9.15 (s) μ.

The Reaction of 2-Mesyloxycyclohexanone with Triphenylphosphine.[19]—A mixture of 2-mesyloxycyclohexanone **19** (11.30 g, 0.0059 mole) and triphenylphosphine (15.49 g, 0.0059 mole) in dry 1,2-dimethoxyethane (25 ml) was refluxed for 5 hr to give 2-ketocyclohexyltriphenylphosphonium mesylate **20** (12.80 g, 48.5%), mp 212.5–214°. The infrared spectrum of **20** (CH_2Cl_2) was similar to that of **16** or **17** and exhibited peaks at 5.83 (m), 6.15 (s), 6.28 (w), 6.68 (m), 6.90 (s), 7.16 (m), 7.32 (w), 7.42 (w), 7.50 (w), 8.05 (m), 8.2–8.35 (s), 8.95 (s), 9.55 (s) and 9.95 (s) μ. Treatment of **20** with 1 *N* aqueous sodium hydroxide gave the keto ylid **18** (76%), mp 215–217°; the infrared spectrum was identical with genuine **18**.

The Reaction of Triphenylphosphine with Mercuric Chloride.[31]—Typically triphenylphosphine to be determined was titrated with mercuric chloride in dry acetone until no further precipitation occurred. This led to quantitative yields of the complex and no triphenylphosphine was left (tlc). If excess mercuric chloride was used the complex occasionally was contaminated by mercuric chloride. Atypically the following experiment established the 1:1 nature of the complex. Triphenylphosphine (0.7928 g, 0.0030 mole) was dissolved in 100 ml of benzene. To this solution was added 3.124 g (0.0115 mole) of mercuric chloride in 25 ml of ethanol to give the complex (2.5855 g, 0.00296 mole if 1:1 $HgCl_2$–PPh_3) and recovered mercuric chloride (2.417 g, 0.0089 mole recovered or 0.0026 mole used). The complex had mp 322–326° and was insoluble in benzene, acetone, petroleum ether, ethyl acetate, and chloroform. *Anal.* Calcd for $C_{18}H_{15}PHgCl_2$: P, 5.80. Found. P, 5.84.

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[31] Unpublished results of H. Parnes and M. Thames, Lehigh University.

Solvent Effects. III. The Influence of Aqueous Dimethyl Sulfoxide on Alkyl Benzoate Ester Saponification Reactions

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The rates of alkaline hydrolysis of seven alkyl benzoate esters have been determined in aqueous dimethyl sulfoxide (DMSO) solvent mixtures of 0.25 to 0.65 mole fraction of DMSO. The rate constant in all cases increases with increasing DMSO content and is well correlated with solvent dielectric constant. The rate constant increase is nearly independent of the alkyl group steric substituent constant but the linear correlation with mole fraction of DMSO readily distinguishes between the branched and nonbranched alkyl benzoate esters. The DMSO catalyst effect is discussed in terms of a solvent cavity model.

The effect of variation of the acyl group in a series of ethyl esters on the saponification rate constant as the dimethyl sulfoxide content of the aqueous DMSO solvent changes was reported in the previous two papers of this series.[1,2] Generally, it was noted that an increase in the steric substituent constant for R was reflected by an enhanced sensitivity to dimethyl sulfoxide catalysis (RCO_2R').

More specifically, it was observed that the dimethyl sulfoxide profile (rate constant *vs.* mole fraction DMSO) for branched R groups is a single linear correlation in contrast to a set of two intersecting linear correlations for the straight-chain esters.

These observations were interpreted largely in terms of solvent assistance to the development of the transition state. For branched esters, electrostatic forces between bulk dielectric[3] and transition state were proposed while a combination of electrostatic and specific solvation forces were associated with the nonbranched esters.[2] The effect of the frequently mentioned[4,5] anion desolvation as the major contributing cause for the rate constant increases was considered to be inconsistent with the data.

The present paper reports the influence of changing R′ upon the dimethyl sulfoxide catalysis effect as a logical continuation of the study. By this means the previous mechanistic speculations can be both confirmed and extended. The choice of alkyl benzoates as the substrate was dictated by several reasons: (a) the convenient rates of reactions over the range

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