Russian Chemical Reviews

Uspekhi Khimii

July 1961

THE WITTIG REACTION

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1. INTRODUCTION

As early as 1919 Staudinger and Meyer[1] discovered the formation of olefines in the reaction of phosphoranes of the type $Ar_3\overset{+}{P}-C\bar{R}'R''$ with carbonyl compounds of the phenylisocyanate type:

$$Ar_3\overset{+}{P}-\bar{C}R'R'' + O=C=NAr \rightarrow ArN=C=CR'R'' + Ar_3PO.$$

However, it was not till 1953 that Wittig and his collaborators[2] established that methylenetriphenylphosphorane, obtained by the reaction of phenyllithium with methyltriphenylphosphonium iodide, reacts with benzophenone to form 1,1-diphenylethylene (84%) and triphenylphosphine oxide (80%). They subsequently[3-6] generalised and developed this reaction into a method for transforming a C=O group into C=C:

$$(C_6H_5)_3\overset{+}{P}-\bar{C}HR + OC\langle \rightarrow \rangle C=CHR + (C_6H_5)_3PO.$$

This reaction has become very important in organic chemistry. It proceeds as a rule in one direction only, and gives high yields of a single product with the double bond in a definite position. For this reason it has a wide field of application in complex organic syntheses. In the synthesis of natural products and their analogues in particular, it has facilitated the solution of some basic problems. Its importance in the chemistry of natural products is brought out by the fact that about 80 out of 100 cases of its application were devoted to the synthesis of natural products and their analogues.

Several reviews on the Wittig reaction have already appeared in foreign periodicals[5-10]. The Soviet literature, however, has not yet dealt with it, apart from a translation of the review by Wittig[5] which appeared in November 1955, and was devoted to the initial stages of the development of this reaction.

In the present review we deal with the applications of the Wittig reaction in the synthesis of natural products (polyacetylenes, terpenes, carotenoids, vitamin A, steroids, vitamin D_2) and their analogues, *i.e.* the field where it has made the most important contributions.

2. ALKYLIDENEPHOSPHORANES

Until recently it was believed that only alkylidenetriphenylphosphoranes(I), where R = C_6H_5, are capable of undergoing the normal Wittig reaction. The view that alkylidenetriphenylphosphoranes are specific reagents in the Wittig reaction was based on theoretical considerations implied by the reaction mechanism put forward by Wittig[2-5]. For example, in 1949 Wittig and Rieber[11] prepared methylenetrimethylphosphorane, treated it with benzophenone, and after neutralising the reaction mixture with acid and adding potassium iodide they obtained a small yield of (β,β-diphenyl-β-hydroxyethyl)trimethylphosphonium iodide. In his systematic study of the Wittig reaction, Johnson[12-15] concluded that fluorenylidenetriphenylphosphorane and fluorenylidenetrimethylphosphorane do not give different reactions with carbonyl compounds, but are distinguished only in their stability and reactivity. This was later confirmed by Trippett and Walker[16], who showed that phosphoranes of type $(CH_3)_n(C_6H_5)_{3-n}\overset{+}{P}-\bar{C}HCOCH_3$, $(CH_3)_n(C_6H_5)_{3-n}\overset{+}{P}-\bar{C}HC_6H_5$ (where n = 0, 1, 2, 3), and $(CH_3)_2(C_6H_5)\overset{+}{P}-\bar{C}HCOOC_2H_5$ react

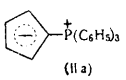
readily with carbonyl compounds, and form normal Wittig reaction products in high yields. These authors also succeeded in causing methylenetrimethylphosphorane to react with benzophenone and, in contrast to the results of Wittig and Rieber [11] (see above), obtained about 40% of 1,1-diphenylethylene, *viz.* the normal reaction product. The Wittig reaction is thus general to alkylidenephosphoranes and is only limited by their stability and reactivity.

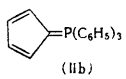
The structure of alkylidenephosphoranes (including alkylidenetriphenylphosphoranes) can be expressed by formula (Ia) or (Ib):

$$\underset{\text{(Ia)}}{R'R''\bar{C}-\overset{+}{P}(R)_3}, \quad \underset{\text{(Ib)}}{R'R''C=P(R)_3},$$

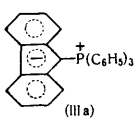
viz. ionic or covalent.

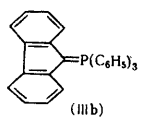
The stability and reactivity towards carbonyl compounds is determined primarily by the distribution of the negative charge in the alkylidenephosphorane molecule, which in turn depends on the nature of substituents R′ and R″ in the alkylidene radical and of substituent R bound to phosphorus. It should be noted that increased stability of a phosphorane lowers its reactivity. The strong carbanion properties of alkylidenephosphorane (Ia) evidently assist its nucleophilic reaction with carbonyl compounds. If for any reason the carbanion character of alkylidenephosphorane decreases, reactivity is reduced. For example, cyclopentadienylidenephosphorane, whose structure is close to the covalent one (IIb), does not react with carbonyl compounds [17,18]:


(IIa)


(IIb)

Fluorenylidenetriphenylphosphorane [13] whose structure is intermediate between ionic (IIIa) and covalent (IIIb), has a markedly low reactivity:


(IIIa)


(IIIb)

Methylenetriphenylphosphorane, where R′ = R″ = H, and no electronic influences lower the carbanion character of the molecule, has a pronounced reactivity [3,4,9]. Accordingly, methylenetriphenylphosphorane is the most unstable of all alkylidenetriphenylphosphoranes. It can be assumed that the substituents R′ and R″ in the carbanion lower the reactivity of alkylidenephosphorane in proportion to their electron-withdrawing capacity.

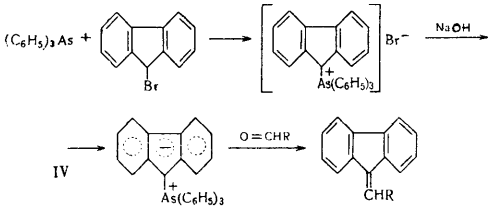
Very relevant to the stability and reactivity of alkylidenephosphoranes is the interaction between the carbanion and the phosphorus atom. The phosphorus atom can expand its octet to a decet, *viz.* form a fifth covalent bond, at the expense of its vacant *d* orbital. This property plays an important role in the chemistry of phosphoranes. In extreme cases the phosphorus atom accepts an electron pair from the *p* orbital of carbon into its *d* orbital, and this results in the establishment of a double bond between phosphorus and carbon (Ib) involving the *d* orbital. The possibility of the formation of multiple bonds was disputed by Jaffe [19-21], who concluded that such bonds are only possible if the central atom is positively charged. Thus, the degree to which the *d* orbital is involved in the reaction with the carbanion depends primarily on the magnitude of the formal positive charge carried by phosphorus. But what determines this charge?

Jaffe [20,21] and Rao [22], with their collaborators, showed in their study of the ultra-violet spectra of the polyphenyl derivatives of tri- and penta-valent phosphorus (in particular of triphenylphosphine and triphenylphosphine oxide) that there is no interaction between benzene rings and the tetracovalent phosphorus atom. However, although there may not be any electronic interaction, the substituents R attached to phosphorus can affect the magnitude of its positive charge by induction. As a result it could be expected that the higher the inductive electron-withdrawing effect (*I*-effect) of the substituent R the more probable is the participation of the *d* orbital in phosphorus in the reaction. This hypothesis is supported by the following data in the literature. Chatt *et al.* [23] studied the ultra-violet and visible spectra of a series of planar complexes of the type *trans*-[*L*, piperidine $PtCl_2$], where the ligands *L* were aliphatic amines, phosphines, etc., and found that the extent of the participation of the phosphorus *d* orbital in the reaction with the metal atom increased in the order $L = P(n\text{-}C_3H_7)_3 < L = P(OCH_3)_3$, which could only be explained by the larger *I*-effect of the methoxy group. Earlier, Chatt and Williams [24] in their study of the "trans effect" of ligands in complexes of trivalent phosphorus established that the π-bonding ability of trivalent phosphorus decreases in the order $PF_3 > PCl_3 > P(OCH_3)_3 > P(n\text{-}C_3H_7)_3$, *viz.* in the same order as the *I*-effect of the substituent. Finally, on the basis of studies of the infra-red spectra of nickelcarbonyldiphosphines [25] and of the compound [26] $L_3Mo(CO)_3$, where $L = PCl_3$, $P(C_6H_5)_3$, etc., it was concluded that the participation of the *d* orbital of phosphorus in the reaction with metal decreases in the order $PCl_3 > P(OC_2H_5)_3 > P(C_6H_5)_3 > P(C_4H_9)_3$, *viz.* in accordance with the *I*-effect.

Thus, alkylidenetrialkylphosphoranes in which the formal positive charge of the phosphorus atom is reduced by the *I*-effect of alkyl substituents should, other conditions being equal, be more reactive than alkylidenetriphenylphosphoranes in which the formal positive charge of the phosphorus atom is increased by the *I*-effect of phenyl rings. This can be illustrated by Johnson's experimental data [15].

Carbonyl compound	% yield of olefine, referred to phosphorane, under similar reaction conditions	
	fluorenylidenetriphenylphosphorane	fluorenylidenetri-*n*-butylphosphorane
CH_3CHO	90	93
p-$O_2NC_6H_4CHO$	96	99
p-ClC_6H_4CHO	93	96
C_6H_5CHO	84	96
p-$CH_3OC_6H_4CHO$	37	94
p-$(CH_3)_2NC_6H_4CHO$	0	94
p-$O_2WC_6H_4COC_6H_4NO_2$-*p*	0	93

Finally, it should be added that the ability to react with carbonyl functions to olefines is not confined to phosphoranes only. Wittig and Henry[27] found that methylenetriphenylarsane reacts with benzophenone to form, among other products, 1,1-diphenylethylene, the normal product of the Wittig reaction. More recently Johnson[14,15] made a thorough study of the reactions of fluorenylidenetriphenylarsane(IV) readily obtained by treating fluorenyltriphenylarsonium bromide with aqueous sodium hydroxide. On boiling with carbonyl compounds in chloroform solution fluorenylidenetriphenylarsane gives high yields of the corresponding olefines:



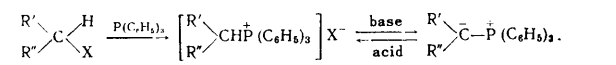
The yields obtained were: R = C_6H_5 (74%); p-$O_2NC_6H_4$ (92%); p-ClC_6H_4 (98%); p-$CH_3OC_6H_4$ (89%); p-$(CH_3)_2NC_6H_4$ (97%); CH_3 (91%).

Fluorenylidenetriphenylarsane is a stable, light-yellow compound which on long boiling with aqueous alcoholic sodium hydroxide yields triphenylarsine oxide. In its stability it is similar to the corresponding phosphorane.

To compare the reactivity of various reagents in the Wittig reaction, Johnson[15] determined the acid pK_a values of some fluorenylidenephosphoranes and obtained: for the triphenylphosphorane 7.5; the triphenylarsane 7.8; the tri-n-butylphosphorane 8.0. The pK_a of the fluorenylidene derivatives therefore decreases in the order triphenylphosphorane > triphenylarsane > tri-n-butylphosphorane, *viz.* in the inverse order of reactivity. Measurements of pK_a can therefore be used to determine the reactivity of the Wittig reagents.

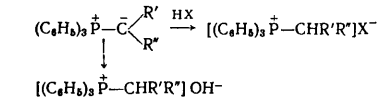
According to their stability and reactivity, Wittig reagents can be divided into three groups. The first and largest group comprises the alkylidenetriphenylphosphoranes, which are characterised by considerable instability and high reactivity. The second group is relatively small, and includes stable yet reactive compounds. Finally, the third group includes a few alkylidenetriphenylphosphoranes having high stability and low reactivity.

Alkylidenetriphenylphosphoranes are prepared from the easily obtained quaternary phosphonium salts according to the scheme

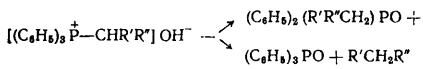


The method for the isolation of phosphoranes from phosphonium salts is chosen according to the group to which a particular phosphorane belongs.

The first group covers mainly phosphoranes containing hydrocarbon radicals in the alkylidene group, which have little or no effect on the carbanion character of the molecule. For example, the following are unstable and reactive triphenylphosphoranes: methylene-, ethylidene-, benzylidene-, cinnamylidene-, etc. These Wittig reagents have a strongly pronounced nucleophilic character and as a result react readily, often in the cold, with carbonyl and other polar groups. The action of hydrogen halides upon these alkylidenetriphenylphosphoranes results in the formation of the initial phosphonium salts, whereas the reaction with water yields hydroxides:

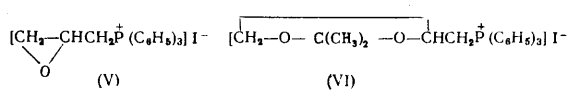


Hydroxides of this type are extremely unstable and decompose irreversibly into diphenylalkylphosphine oxide and benzene or triphenylphosphine oxide and alkane:



For this reason the alkylidenetriphenylphosphoranes of the first group are highly sensitive to moisture and usually cannot be prepared from phosphonium salts using alkali hydroxides.

In rare cases the Wittig reagents of the first group are so reactive that during preparation they undergo secondary reactions. For instance, Bohlmann and Herbst[28] could not obtain phosphoranes from phosphonium salts of type (V) and (VI) owing to the extreme instability of the products formed



The second group of Wittig reagents comprises compounds which contain, in the alkylidene radical, atoms or groups with electron-withdrawing properties, for instance acyl or ethoxycarbonyl groups. These do not, however, appreciably affect the carbanion character of the molecule, nor consequently, its reactivity. Acetylmethylene-[29] and ethoxycarbonylmethylene-triphenylphosphoranes[3], for instance, are colourless crystalline compounds which can be kept for a long time without change. The Wittig reagents of the second group react relatively readily with a number of carbonyl compounds. In contrast to the reagents of the first group, however, they do not react with ketones, as was observed, for example, in the reaction of ethoxycarbonylmethylenetriphenylphosphorane with the diethyl acetal of acetoacetic aldehyde[30]. Nor do alkylidenetriphenylphosphoranes of this type react with water, so that no precautions to exclude moisture are needed.

A typical representative of the third group is cyclopentadienylidenetriphenylphosphorane, which is a yellow crystalline substance, m.p. 229°–231°, which does not react with benzophenone, fluorenone, cyclohexanone, and other ketones on boiling in ether, chloroform, alcohol, or tetrahydrofuran for 120 h.[17,18] Although it apparently reacts with benzaldehyde[17], no pure reaction product could be isolated.

The unusual stability of this phosphorane, as already pointed out, is a result of the formation of a covalent bond between phosphorus and carbon with the participation of the vacant *d* orbital in phosphorus.

Fluorenylidenetriphenylphosphorane[13] is an interesting example of a compound similar in structure to cyclopentadienylidenetriphenylphosphorane, but in which the tendency for the formation of such a bond is considerably lower. It

is nearly as stable as cyclopentadienylidenetriphenylphosphorane, and like this compound it does not react with acetone, cyclohexanone, fluorenone, and *p*-dimethylaminobenzaldehyde. Nevertheless, it reacts with benzaldehyde, *p*-methoxybenzaldehyde, *p*-nitrobenzaldehyde, and 2,4,7-trinitrofluorenone, giving the corresponding 9-arylmethylenefluorenes in 84–100% yield. Compounds of this group do not hydrolyse even on prolonged boiling in water.

It follows, therefore, that the use of the Wittig reaction in organic synthesis for the introduction of alkylidene groups is confined to reagents of the first and second (occasionally of the third) group. The application of the method is also limited by the reactivity of the reagents towards carbonyl functions.

Mention may be made of a recent new method[31] for the synthesis of alkylidenetriphenylphosphoranes, *viz.* formylalkylidenephosphoranes of the type $(C_6H_5)_3\overset{+}{P}-\overline{C}(R)CHO$, by the reaction of methylenetriphenylphosphorane with an excess of ethyl formate:

$$R\bar{C}H-\overset{+}{P}(C_6H_5)_3 + HCOOC_2H_5 \rightarrow (C_6H_5)_3\overset{+}{P}-\bar{C}(R)CHO + C_2H_5OH,$$

where R = H, C_2H_5.

Formylalkylidenetriphenylphosphoranes belong to the second group of Wittig reagents and react normally with aldehydes on boiling in benzene solution. For example:

$$RCHO + (C_6H_5)_3\overset{+}{P}-\bar{C}HCHO \rightarrow (C_6H_5)_3PO + RCH=CHCHO,$$

where R = C_6H_5, yield 60%, R = *n*-C_7H_{15}, yield 81%.

It should be noted, however, that like ethoxycarbonylmethylenetriphenylphosphorane, formylmethylenetriphenylphosphorane does not react with ketones.

Methods of preparing quaternary phosphonium salts and, hence, alkylidenetriphenylphosphoranes, are given below.

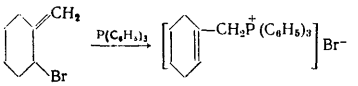
Phosphonium salts are prepared, according to the nature of the organic halide, by one of the following three methods:

1. heating triphenylphosphine with excess halide[32,33];
2. dissolving triphenylphosphine with an equimolar quantity of halide[33,34];
3. reacting equimolar quantities of triphenylphosphine and halide at or above room temperature in a suitable solvent[1,33].

The first two methods are rarely used, and then mainly for the preparation of phosphonium salts which are difficult to obtain. For instance, by heating triphenylphosphine with excess of 1,2-dibromoethane, 1,3-dibromopropane, or 1,4-dibromobutane at 150°–180° Wittig *et al.*[32] obtained bis-phosphonium salts of the type $[(C_6H_5)_3\overset{+}{P}(CH_2)\overset{+}{P}(C_6H_5)_3]2Br^-$ in 80 to 90% yields. Mondon[34] obtained the bis-phosphonium salt $[(C_6H_5)_3\overset{+}{P}(CH_2)_4\overset{+}{P}(C_6H_5)_3]2Br^-$ in 80% yield by melting at 250° the monophosphonium salt $[(C_6H_5)_3\overset{+}{P}(CH_2)_3.CH_2Br]Br^-$ with triphenylphosphine.

The third method, which is most widely used, is simple, convenient, and flexible. Ether and benzene[3] are most often used as solvents, toluene and xylene[33,35] and chloroform[33] less so. For phosphonium salts which are difficult to obtain, the use of highly polar solvents is recommended (nitromethane, nitrobenzene, and especially dimethylformamide[10,33]). For instance, boiling triphenylphosphine with 1,4-dichloro-2-butene or ω,ω′-dibromo-*m*-xylene in ether solution gives a mixture of mono- and bis-phosphonium salts; in chloroform, only the bis-phosphonium salts are obtained, in low yield; using nitrobenzene or dimethylformamide enables almost quantitative yields of bis-phosphonium salts to be obtained[33].

It should be noted that the formation of phosphonium salts from allyl halides is sometimes complicated by allylic rearrangement[36]:



Triphenylphosphine can react with various primary and secondary mono- and di-halogen derivatives: aliphatic saturated halides (methyl chloride, methyl bromide, or methyl iodide[2,3], isoamyl bromide[37] or iodide[38], n-dodecyl bromide[39], 1,2-dibromoethane[32], etc.), aliphatic-aromatic halides (benzyl chloride[40] or bromide[3], ω,ω′-dichloro-*p*-xylene[41], etc.), halides of the type of 9-bromofluorene[14], and various unsaturated halides (allyl bromide[3,42], cinnamyl bromide[40], 1-bromo-2,8-decadiene-4,6-diyne[42], geranyl bromide[43], cyclogeranyl bromide[43]). A most important feature of phosphonium salts is that they are capable of being formed from various halogen derivatives containing functional groups, *e.g.* haloketones (bromoacetone[29], ω-bromoacetophenone[29]), esters of halogen-substituted carboxylic acids (ethyl α-bromoacetate[3], methyl 4-bromocrotonate[44], etc.), and halogen-substituted ethers (α-chlorodimethyl ether[45]). The reaction rate decreases in the order iodide > bromide > chloride. The bromides are more commonly used, as they are easier to obtain.

In certain cases the success of the Wittig reaction depends on the kind of phosphonium salt (iodide, bromide, or chloride) used for the preparation of phosphorane. For example, Collins and Hammond[46] were unable to obtain methylenecyclopentane using the Wittig reagent prepared from methyltriphenylphosphonium iodide.

The most important stage in the development of the Wittig reaction was the preparation of alkylidenetriphenylphosphoranes from phosphonium salts. We discussed above the structure, stability, and reactivity of Wittig reagents. Methods for preparing alkylidenetriphenylphosphoranes from phosphonium salts depend entirely on the nature of the resulting phosphorane. The unstable alkylidenetriphenylphosphoranes, which belong to the first group, must be prepared in an anhydrous medium by reactions involving organometallic compounds, which serve as proton-acceptors. Most frequently a suspension of phosphonium salt in ether, tetrahydrofuran, or some other suitable solvent is treated with an ether solution of an equimolar amount of phenyl- or butyl-lithium, in a dry nitrogen atmosphere[3,4]. The reaction usually proceeds in the cold, and the formation of alkylidenetriphenylphosphorane can be observed from the appearance of an orange or cherry coloration. The carbonyl compound is subsequently introduced and the mixture is heated, if necessary, whereupon the colour gradually disappears. A variation of this procedure is the preparation of alkylidenetriphenylphosphorane by treating a suspension of phosphonium salt in liquid ammonia with sodamide and subsequently replacing the ammonia by ether or tetrahydrofuran. The preparation of phosphoranes by the action of alkali acetylides on a solution of phosphonium salt in dimethylformamide has also been described[47,48]. Since many phosphonium salts are conveniently prepared in dimethylformamide (see above), this variant of the Wittig reaction reduces to one stage only, without isolation of the quaternary salt.

In another method for the preparation of alkylidenetriphenylphosphoranes from phosphonium salts, sodium, potassium, or lithium ethoxide, or methoxide is used as proton-acceptor[3,10,40]. This method can be used for the preparation of stable phosphoranes of the second and third groups, as well as for some of the more stable phosphoranes of the first group, *e.g.* from bis-phosphonium salts. Mondon[34] used this method for the preparation of $(C_6H_5)_3\overset{+}{P}-\bar{C}H(CH_2)_2\bar{C}H-\overset{+}{P}(C_6H_5)_3$ from the appropriate bis-phosphonium salts, and Campbell and McDonald[41] for the preparation of bis-phosphorane from *p*-xylylene-bis-(triphenylphosphonium chloride). The reaction with unstable phosphoranes is carried out by adding an alcoholic solution of the equivalent amount of an alkali metal alkoxide to the mixture of the phosphonium salt and the carbonyl compound in alcohol, dimethylformamide, alcohol–methylene chloride, or alcohol–dimethylformamide[10].

Finally, the most suitable method for the preparation of stable phosphoranes of the second and third groups is the reaction of aqueous solutions of the phosphonium salt and alkali[49]. The resulting phosphorane forms a crystalline precipitate which after drying in the air can immediately be used in the reaction. The condensation of a stable phosphorane with carbonyl compounds is usually carried out in boiling benzene, tetrahydrofuran, chloroform, or other solvents.

One possible complication in the preparation of bis-phosphoranes from bis-phosphonium salts is the splitting off of triphenylphosphine. For instance, this was observed during the treatment of bis-phosphonium salt obtained from 1,2-dibromoethane and triphenylphosphine with an ether solution of phenyllithium[10]:

$$[(C_6H_5)_3\overset{+}{P}CH_2CH_2\overset{+}{P}(C_6H_5)_3]\ 2Br^- \xrightarrow{C_6H_5Li} [(C_6H_5)_3\overset{+}{P}-CH=CH_2]\ Br^- + (C_6H_5)_3P.$$

The resulting compound was vinyltriphenylphosphonium bromide.

A similar phenomenon was observed during the reaction of an ether solution of phenyllithium with the quaternary salt obtained from 1,4-dibromo-2-butene:[10]

$$[(C_6H_5)_3\overset{+}{P}CH_2CH=CHCH_2\overset{+}{P}(C_6H_5)_3]\ 2Br^- \xrightarrow{C_6H_5Li} [(C_6H_5)_3\overset{+}{P}CH=CHCH=CH_2]\ Br^- + (C_6H_5)_3P.$$

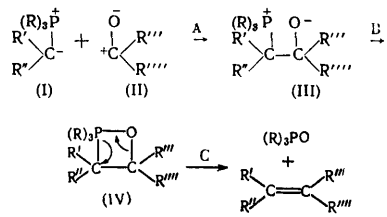
These cases illustrate the need to use alkali metal alkoxides in the preparation of bis-phosphoranes.

An interesting case is the decomposition of alkylidenetriphenylphosphorane to form a cyclic product[34]:

$$[(C_6H_5)_3\overset{+}{P}(CH_2)_3CH_2Br]\ Br^- \xrightarrow{C_6H_5Li} (C_6H_5)_3\overset{+}{P}-\bar{C}HCH_2CH_2CH_2Br \rightarrow$$
$$\rightarrow [(C_6H_5)_3\overset{+}{P}-\underset{\displaystyle CH_2-CH_2}{\overset{\displaystyle |\quad\quad|}{CH}}]\ Br^-.$$

3. MECHANISM AND STEREOCHEMISTRY OF THE WITTIG REACTION

According to Wittig and Schöllkopf[3] the formation of olefines in the reaction of alkylidenetriphenylphosphoranes with carbonyl functions proceeds as follows:



In the first place the alkylidenetriphenylphosphorane (I) (where R = C_6H_5) reacts with the polarised carbonyl group in a carbonyl compound (II) forming a betaine (III). If the phosphorus atom shows a tendency to expand its external electron shell to a decet, and if the steric factors allow it, an electron pair from the oxygen will attach itself to the phosphorus atom. A four-membered ring is formed (IV) and subsequently decomposes into triphenylphosphine oxide and olefine, either spontaneously or on heating.

The success of the Wittig reaction depends on the success of the three reaction stages (A, B, and C). Stage A is made easier by the presence of a highly polarised carbonyl group, or, with less strongly polar carbonyl compounds, by the high reactivity of phosphorane.

The formation of betaine (III) in the first stage of the reaction has been proved by the isolation of a stable betaine in the reaction of methylenetriphenylphosphorane with benzaldehyde:

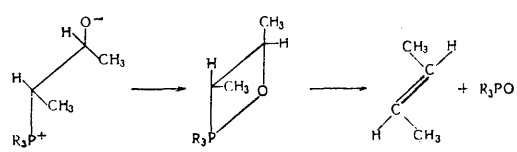
$$(C_6H_5)_3\overset{+}{P}-\bar{C}H_2 + C_6H_5CHO \rightarrow (C_6H_5)_3\overset{+}{P}CH_2\underset{\displaystyle \bar{O}}{\overset{\displaystyle |}{C}}HC_6H_5 \xrightarrow{HBr}$$
$$\rightarrow [(C_6H_5)_3\overset{+}{P}CH_2CH(OH)C_6H_5]\ Br^-$$

Betaine is characterised as its crystalline hydrobromide, which is converted back into betaine by the action of RLi. An ether suspension of the betaine, heated at 60°–65° for several hours, decomposes into triphenylphosphine oxide (91%) and styrene (67%).

The formation of the same betaine was postulated by Wittig and Haag[4] for the reaction of styrene oxide with triphenylphosphine, which, carried out at 165°, yields styrene (50%) and triphenylphosphine oxide:

$$(C_6H_5)_3P + \underset{\displaystyle C_6H_5HC}{\overset{\displaystyle H_2C}{\diagdown O\diagup}} \rightarrow \underset{\displaystyle \bar{O}-CHC_6H_5}{\overset{\displaystyle (C_6H_5)_3\overset{+}{P}-CH_2}{|}} \rightarrow (C_6H_5)_3PO + C_6H_5CH=CH_2$$

Boskin and Denney[50] made a study of this reaction with the oxides of *trans*-2-butene and *cis*-2-butene, using tributylphosphine. They showed that the *trans*-oxide yielded a mixture of 72% *cis*-2-butene and 28% *trans*-2-butene, whereas the *cis*-oxide yielded a mixture of 81% *trans*-2-butene and 19% *cis*-2-butene. Under their reaction conditions (150°) the spontaneous isomerisation of the olefines amounted to less than 2%. Their work therefore confirmed the reaction mechanism previously suggested by Wittig:



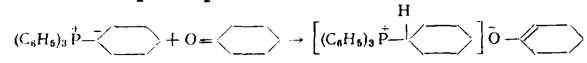
While the decomposition of betaine yields the primary product in the reaction mixture, the mechanism of the formation of the second product is still not clear.

It should be noted that the first stage (A) of the Wittig reaction is reversible, which is confirmed by the increased yield of olefine on raising the amount of alkylidenetriphenylphosphorane above the theoretical.

The mechanism of the third stage (C) is not clear, since the kinetic aspects of the Wittig reaction have not yet been studied.

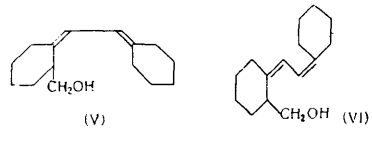
Wittig[3,5,6] considered that the overall success of the reaction is determined by stage B, namely by the transformation of the betaine (III) into the four-membered ring (IV). He thought that the reaction would stop at the betaine stage if, through steric or electronic factors, the ring (IV) could not be formed. Hence he argued that alkylidenetrialkylphosphoranes are unable to react with carbonyl compounds to give olefines because the cyclisation of betaine (III) (where R = alkyl) into the intermediate ring (IV) is made impossible by the inductive effect of alkyl groups, which prevent any attack of oxygen on phosphorus. In the light of the most recent work by Johnson[13-15] and Trippet[16], however, these arguments appear irrelevant, since there is no inductive effect of alkyl groups and no suppression of the attack by oxygen on phosphorus, and alkylphosphoranes undergo Wittig reaction with the same ease as alkylidenetriphenylphosphoranes. Johnson[15] considers stage A to be the most important, and stage B to be affected by steric factors only.

In the reaction with enolisable ketones, alkylidenetriphenylphosphoranes (especially those with sterically hindered molecules) may form enolates instead of addition products with the carbonyl group. This side-reaction is sometimes the principal one. For instance[10]:

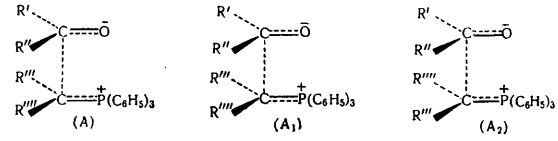


Unsymmetrical alkylidenetriphenylphosphoranes and carbonyl compounds generally yield mixtures of *cis*- and *trans*-isomers. For instance, a suspension of vinylmethylenetriphenylphosphorane in ether and benzaldehyde, heated at 65°, gives 58% 1-phenyl-1,3-butadiene[2] as a 1:1 mixture of *cis*- and *trans*-isomers. In a number of cases, however, *trans*-isomers are the predominant or the exclusive products. The reaction of benzylidenetriphenylphosphorane with benzaldehyde gave 82% stilbene, which consisted of 70% *trans*- and 30% *cis*-isomer. Most frequently, only *trans*-isomers are formed in the synthesis of natural products (lycopene, β-carotene, etc.). Cases with *cis*--isomer predominating in the reaction mixture (up to 80%) have also been reported[39].

No systematic study of the stereochemistry of the Wittig reaction has yet been made, nor has the effect of changes in reaction conditions upon the ratio of *cis*- and *trans*-isomers been elucidated, although such an effect is recognised. Indeed, the reaction of (*o*-hydroxymethylcyclohexylidene)-ethylidenetriphenylphosphorane with cyclohexanone in tetrahydrofuran solution at -25° yields almost entirely the *cis*--diene (V), while at room temperature the reaction mixture contains a considerable amount of the *trans*-isomer (VI).[51]



Levisalles[9] attempted in a number of cases to explain the stereospecificity of the reaction. He considers that the steric structure of the resulting olefine $R'R''C=CR'''R''''$ depends on the transition state which precedes the formation of betaine. According to Levisalles, the transition state (A), where the dipoles $\overset{+}{C}-\bar{O}$ and $\bar{C}-\overset{+}{P}$ are arranged so that the electrostatic interaction between them is at a minimum, is the most probable. This state is subjected to two mutually opposing forces: 1) the transfer of electrons from oxygen to phosphorus (O → P), resulting in the formation of the four-membered ring, and 2) the tendency to rotation about the C–C axis, which is a result of the mutual repulsion of the uncombined carbon atoms. Since the transfer of electrons proceeds faster than that of atoms, the steric structure of the four-membered ring and of the resulting olefine is determined by the transition state (A). Depending on the volume of the substituents R', R'', R''', and R'''' and on their polarity, the preferred transition state (A_1 or A_2) is the one in which the interaction between the uncombined atoms is smallest, and the bulkiest groups in the intermediate four-membered ring take up position in which they are farthest apart:



Therefore, the largest groups in the resulting olefine are placed in *trans*-position. The exclusive formation of *trans*-isomers in a number of cases may be attributed to the unfavourable steric relations in the *cis*-position of the transition state, which increases the energy barrier of the reaction or causes the dissociation of A into the starting components.

4. SYNTHESIS OF NATURAL POLYACETYLENIC COMPOUNDS

It has recently been shown that compounds containing triple bonds are widely distributed in plants. A systematic study of such compounds revealed that in a number of cases they have remarkable biological properties (antibiotic activity at high dilution, strong toxic properties, etc.). This stimulated a number of research workers to work out methods for the synthesis of polyacetylenes similar to, or identical with the natural ones, with a view to a thorough investigation of their physiological activity.

The most difficult task in the synthesis of any highly unsaturated chain of carbon atoms is the introduction of the double bond of a definite configuration in a strictly fixed position. Most of the earlier methods for the introduction of the double bond resulted in a mixture of geometrical or steric isomers. That is why Wittig reaction, which facilitates the introduction of the double bond in a predetermined position (as a rule, in a stereospecific manner), and which is at the same time a powerful means for lengthening the carbon chain by a group of desired structure, has aroused great interest among those working on polyacetylenes.

It was shown in a number of papers by Bohlmann and his collaborators[28,40,42,44,52-61] that the Wittig reaction can be widely and successfully used in the synthesis of polyenynes. The most interesting examples of the application of this

reaction in the synthesis of natural polyacetylenic compounds are the syntheses of oenanthetol[52,60], isolated from *Oenanthe crocata*, of cicutol[53] from *Cicuta virosa*, of anacycline[56], the natural insecticide from the roots of *Anacyclus pyrethrum*, and of aethusanol B[61] from *Aethusa cynapium* L.

The Wittig reaction was used in the synthesis of oenanthetol for the preparation of 3,5-dodecadien-1-yne (I). The oxidative condensation of (I) with 3-penten-1-yn-5-ol (II) in the presence of cuprous chloride gave 14.1% oenanthetol. To prepare (I), the phosphonium salt (III) obtained in 44% yield from 1-bromo-2-nonene and triphenylphosphine, was treated with the solution of n-butyllithium in oil, and to the resulting solution of 2-nonenylidenetriphenylphosphorane, propargyl alcohol was added. The yield of the final enyne (I) was 43%.

$$BrCH_2CH{=}CHC_6H_{13}\text{-}n + (C_6H_5)_3P \rightarrow [(C_6H_5)_3\overset{+}{P}CH_2CH{=}CHC_6H_{13}]\overset{-}{Br} \xrightarrow{C_4H_9Li} \underset{(III)}{\cdot}$$

$$\rightarrow (C_6H_5)_3\overset{+}{P}\text{—}\overset{-}{C}HCH{=}CHC_6H_{13}\text{-}n \xrightarrow{HC\equiv CCHO}$$

$$\rightarrow HC{\equiv}C(\underset{(I)}{CH_3{=}CH)_2}C_6H_{13}\text{-}n \xrightarrow{HC\equiv CCH{=}CHCH_2OH\ (II)}$$

$$\rightarrow \underset{\text{oenanthetol}}{n\text{-}C_6H_{13}(CH{=}CH)_2(C{\equiv}C)_2CH\text{—}CHCH_2OH}\ .$$

A similar reaction scheme was used to obtain cicutol:

$$n\text{-}C_4H_9CH{=}CHCH_2Br + (C_6H_5)_3P \xrightarrow{70\%} [(C_6H_5)_3\overset{+}{P}CH_2CH{=}CHC_4H_9\text{-}n]Br^- \rightarrow$$

$$\xrightarrow{C_4H_9Li} (C_6H_5)_3\overset{+}{P}\text{—}\overset{-}{C}HCH{=}CHC_4H_9\text{-}n \xrightarrow{HC\equiv CCH{=}CHCHO}$$

$$\rightarrow n\text{-}C_4H_9(CH{=}CH)_3C{\equiv}CH \xrightarrow[8.3\%]{HC\equiv CCH_2CH_2CH_2OH}$$

$$\rightarrow \underset{\text{cicutol}}{n\text{-}C_4H_9(CH{=}CH)_3\ (C{\equiv}C)_2CH_2CH_2CH_2OH}\ .$$

For the synthesis of anacycline, the phosphonium salt obtained in 90% yield from decadiynyl bromide (IV) was converted to the phosphorane (V) by butyllithium. This reacted with the methyl ester of 2-buten-1-al-4-oic acid (VI) to give 47% of the key methyl ester of 2,4-tetradecadiene-8,10-diyn-1-oic acid (VII); (VII) was saponified and converted to the acid chloride by thionyl chloride. Treatment of the acid chlorides with isobutyl amine gave anacycline, *viz.* the isobutylamide of 2,4-tetradecadiene-8,10-diyn-1-oic acid.

$$\underset{(IV)}{n\text{-}C_3H_7(C{\equiv}C)_2(CH_2)_2CH_2Br} + (C_6H_5)_3P \xrightarrow{90\%} [C_3H_7(C{\equiv}C)_2(CH_2)_3\overset{+}{P}(C_6H_5)_3]Br^- \rightarrow$$

$$\xrightarrow{C_4H_9Li} \underset{(V)}{C_3H_7(C{\equiv}C)_2CH_2CH_2\overset{-}{C}H\text{—}\overset{+}{P}(C_6H_5)_3} \xrightarrow[47\%]{H_2COOCCH{=}CHCHO\ (VI)}$$

$$\rightarrow \underset{(VII)}{C_3H_7(C{\equiv}C)_2(CH_2)_2(CH{=}CH)_2COOCH_3} \xrightarrow[3.\ (CH_3)_2CHCH_2NH_2]{1.\ KOH;\ 2.\ SOCl_2}$$

$$\rightarrow \underset{\text{anacycline}}{C_3H_7(C{\equiv}C)_2CH_2CH_2(CH{=}CH)_2CONHCH_2CH(CH_3)_2}\ .$$

The Wittig reaction was also used for the preparation of polyenynes required in the synthesis of natural polyacetylenes isolated from various species of *Corlopsis*, *Artemisia vulgaris*, *Centaurea ruthenica*, etc. They include 3,5-hexadien-1-yne[55] (from propargyl aldehyde and vinylmethylenetriphenylphosphorane); 3,5,11-dodecatrien-1-yne[58] (from propargyl aldehyde and 1,7-nonadienylidenetriphenylphosphorane, in 53% yield), 1,3,5,11-tridecatetraene-7,9-diyne[42] (from 2,8-dodecadiene-4,6-diyn-1-al and vinylmethylenetriphenylphosphorane in 50% yield), 8,10,16-heptadecatriene-2,4,6-triyne,[51] 2,2,15,15-tetramethyl-7,9-hexadecadiene-3,5,11,13-tetrayne,[57] etc.

By using appropriate aldehydes and alkylidenetriphenylphosphoranes, the Wittig reaction can thus be used for preparing a great variety of substituted polyenynes, the limiting factor being only the availability of the starting compounds.

In the majority of cases the yields of the required substances are satisfactory (40–60%). However, polyenynes are sometimes formed in very low yields. For instance, the condensation of acrolein with 2,8-decadiene-4,6-diynylidenetriphenylphosphorane[42] gave only 5% 1,3,5,11-tridecatetraene-7,9-diyne (as a mixture of *cis*- and *trans*-isomers), and 1-phenyl-7-nonaene-1,3,5-triyne-9-al with ethylidenetriphenylphosphorane gave a low yield of 1-phenyl-7,9-undecadiene-1,3,5-triyne.

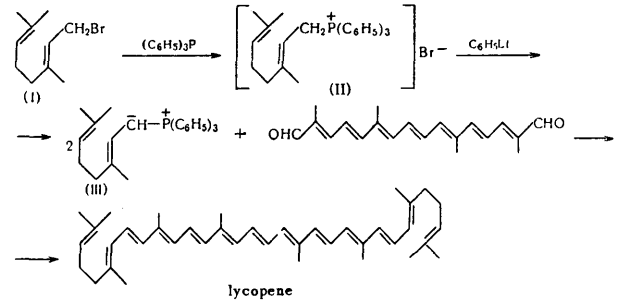
The Wittig reaction is an invaluable method for the synthesis of polyynes and polyenynes. Its potentialities have by no means been fully exploited in the field of natural polyacetylenes: in many cases no attempt was made to increase the yield by varying the experimental conditions.

5. SYNTHESIS OF TERPENES, CAROTENOIDS, AND VITAMIN A

In the field of terpenes, carotenoids, and vitamin A, whose synthetic preparation has till recently been very laborious and complicated, the Wittig reaction has opened new horizons. Its importance in the synthesis of carotenoids and vitamin A was first noted by Wittig himself[5] in 1954. Since then the Wittig reaction has acquired practical importance in isoprenoid chemistry, as is borne out by the ever-increasing number of patents issued for its application to the synthesis of useful substances such as vitamin A, β-carotene, vitamin A acid, etc.

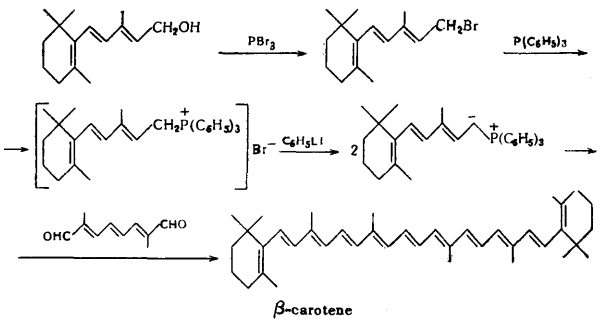
The Wittig reaction made possible the simple synthesis of symmetrical carotenoid hydrocarbons from isoprenoid bromides, which are easy to obtain, and the relatively accessible dialdehydes.

Isler and collaborators[62,63] used the Wittig reaction in the simplest synthesis of lycopene (the natural pigment in tomatoes) yet available. They reacted phosphorus tribromide with linalool (linalool is now produced on an industrial scale) and obtained geranyl bromide (I), which reacted even in the cold with triphenylphosphine forming a crystalline phosphonium salt (II) in high yield. By treatment of (II) with phenyllithium a red solution of geranylidenetriphenylphosphorane (III) was obtained, which reacted readily with crocetindialdehyde to give lycopene, identical with the natural pigment, in about 70% yield.



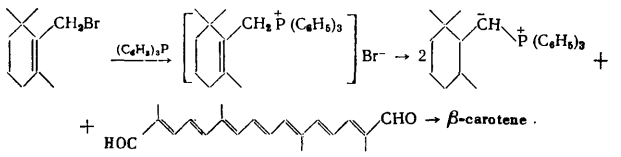
Likewise, 2,2'3,3'-tetrahydrolycopene[63,64] was obtained from 6,7-dihydrogeranylidenetriphenylphosphorane and crocetinaldehyde, and 15,15'-dehydrolycopene from geranylidenetriphenylphosphorane and 8,8'-dehydrocrocetindialdehyde[62-65].

A very interesting and convenient method for the preparation of β-carotene (the widely distributed plant pigment, which is pro-vitamin A) was developed by Wittig and Pommer[47] using the readily available β-ionylideneethanol, *via* the corresponding bromide and phosphorane. Their synthesis differs from the earlier ones by the small number of stages involved, and certainly has possibilities for the industrial preparation of β-carotene.



β-carotene

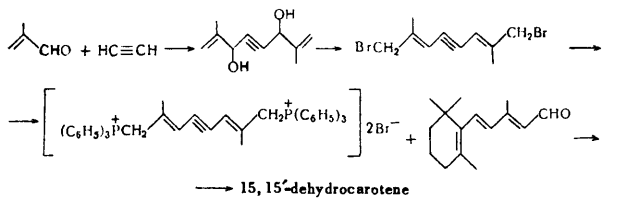
An even simpler scheme was described in a patent[66].



It should be noted that 2,6,11,15-tetramethyl-2,4,6,8,10,12,14--hexadecaheptaene-1,16-dial, which is used in this synthesis, is readily available.

15,15'-Dehydro-β-carotene was obtained similarly by the condensation of β-ionylideneethylidenetriphenylphosphorane with 2,7-dimethyl-2,6-octadien-4-yne-1,8-dial,[47] or of β-cyclogeranylidenetriphenylphosphorane with 8,8'--dehydrocrocetindialdehyde[62].

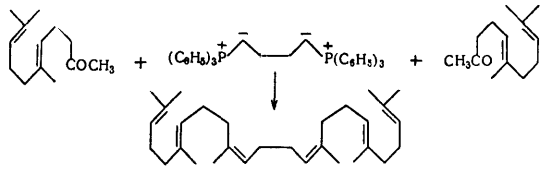
Surmatis and Ofner[67] carried out an interesting variation of the synthesis of 15,15'-dehydro-β-carotene:



15,15'-dehydrocarotene

These authors used the same scheme for the synthesis of β-carotene itself and of decapreno-β-carotene.

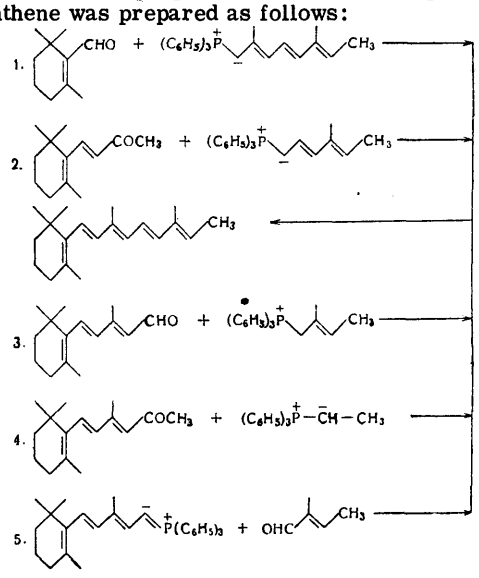
The best example of the successful use of the Wittig reaction in the synthesis of symmetrical isoprenoid hydrocarbons is the synthesis of squalene, the aliphatic triterpenic hydrocarbon constituent of living organisms and the precursor of steroids. A somewhat different principle from the one used in the synthesis of β-carotene was used in the case of squalene. Whereas the synthesis of β-carotene was carried out by the condensation of phosphorane with the symmetrical dialdehyde of appropriate structure, in the synthesis of squalene the symmetrical diphosphorane, prepared from 1,4-dibromobutane, was condensed with geranylacetone[34,68-70]. Squalene was isolated from the reaction mixture in 26% yield. This was the first synthetic squalene identical with the natural one. The methods used previously gave complex mixtures, from which it was possible to isolate pure squalene. The above synthesis of squalene is, like that of β-carotene, very simple and practicable.



squalene

Squalene labelled with ^{14}C in positions 11 and 14, which is very important in the study of steroid biosynthesis in the living organisms, has been synthesised[71] similarly, from 1,4-dibromo[2,3-^{14}C]butane. This method was also used in the synthesis of 3,8-dimethyl-3,5,7-decatriene-1,9-diyne,[72] an important intermediate in the synthesis of many carotenoids.

The Wittig reaction was also used in the preparation of unsymmetrical isoprenoid hydrocarbons, in particular axerophthene, the hydrocarbon with a vitamin A skeleton[73-75]. This example illustrates the flexibility of the Wittig reaction, which can use the most varied starting compounds for the preparation of the same product. Axerophthene was prepared as follows:



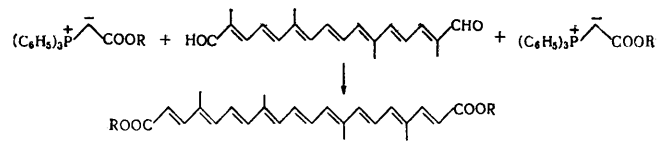
During his study of the stereochemistry of phytol, geraniol, and nerol, Burrell[76] treated *DL*-6, *D'*-10,14-trimethylpentadecan-2-one with methylenetriphenylphosphorane and obtained the corresponding hydrocarbon.

The application of the Wittig reaction to isoprenoid chemistry is not limited to hydrocarbons. Using phosphoranes prepared from the halogen derivatives of acids, a convenient and simple method has been devised for introducing the carboxyl group into the polyene chain, thus providing an easy path to the carotenoid and other polyenic acids.

The introduction of the methyleneethoxycarbonyl group has been widely applied. It proceeds by the general scheme:

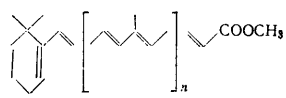
$$RCHO + (C_6H_5)_3\overset{+}{P}-\overset{-}{C}HCOOC_2H_5 \rightarrow RCH=CHCOOC_2H_5.$$

Isler and collaborators[49] used this reaction scheme in the condensation of crocetindialdehyde with alkoxycarbonylmethylenetriphenylphosphoranes and prepared a number of bixin esters:



bixin (where R = H)

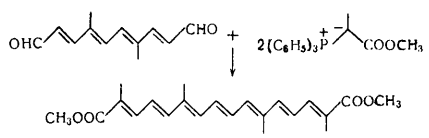
The condensation of methoxycarbonyltriphenylphosphorane with 15,15′-dehydro-β-apo-12′-carotenal (C_{25}) and its vinylogues up to 15,15′-dehydro-β-apo-2′-carotenal (C_{37}) was used [77-80] in the first reported preparations of the methyl ester of 15,15′-dehydro-β-apo-10′-carotenic acid (C_{27}) and its vinylogues up to the methyl ester of 15,15′-dehydro-β-apo-2-carotenic acid (C_{37}). Partial hydrogenation of the latter gave the corresponding methyl esters of β-apo-carotenic acids



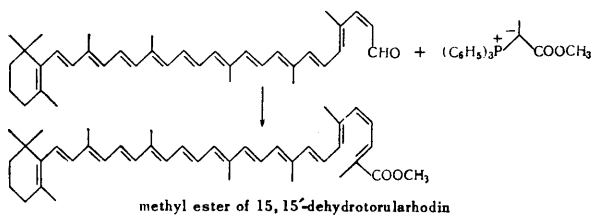
where $n = 3,4,5$.

The previously available methods for the introduction of a carboxyl group were not well suited to the synthesis of such highly unsaturated acids.

By using α-alkoxycarbonylethylidenetriphenylphosphoranes obtained from the esters of β-bromopropionic acid it is possible to introduce not only a methylenecarboxyl group, but also a side methyl group. Isler and collaborators [49,77-80] made use of this possibility in their synthesis of the dimethyl ester of crocetin, methyl ester of 15,15′-dehydrotorularhodin and its vinylogues according to the scheme:



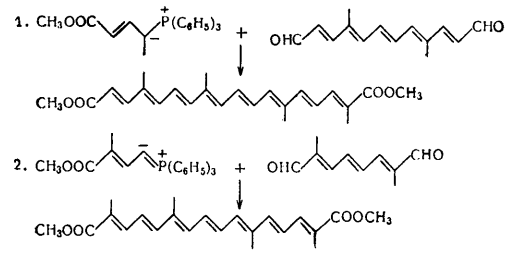
dimethyl ester of crocetin



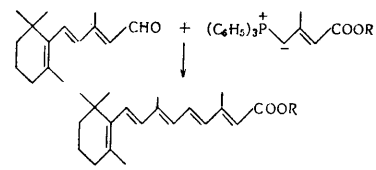
methyl ester of 15, 15′-dehydrotorularhodin

Partial hydrogenation, isomerisation, and saponification of the methyl ester of 15,15′-dehydrotorularhodin gave the carotenoid torularhodin, identical with the natural material isolated from *Rhodotorula mucilaginosa*. Its structure was thus confirmed by synthesis. This was one of the great successes of the Wittig reaction.

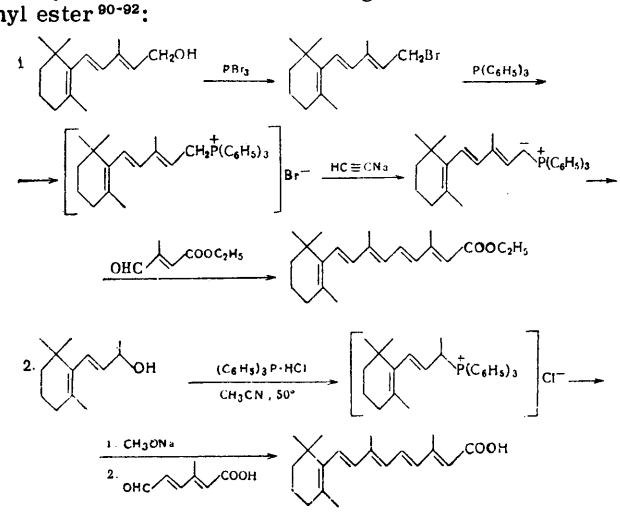
Buchta and Andree's [81-84] recent preparation of isoprenoid and other unsaturated acids from phosphoranes obtained from ω-haloacids offers several interesting possibilities. These workers suggested new methods for the synthesis of dimethyl ester of bixin and crocetin, and of dimethyl ester of 4,4′-desmethylbixin by the condensation of phosphoranes prepared from the methyl esters of γ-bromocrotonic or γ-bromotiglic acids with the appropriate dialdehydes according to the scheme:



Analogous methods for the preparation of the esters of vitamin A acid were patented [73,85-87]. For instance:



For the Wittig synthesis of the esters of vitamin A acid, the condensation of phosphoranes with aldehydic acids is preferable [88-93]. For instance, condensation of the phosphorane prepared from β-ionylideneethanol, *via* the corresponding chloride or bromide, with the ethyl ester of 3-methyl-2-buten-4-al-1-oic acid gave vitamin A acid ethyl ester [90-92]:



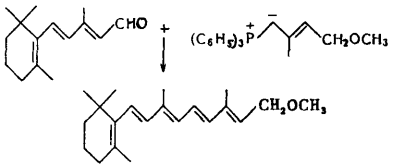
Vitamin A acid methyl ester was also prepared by the reaction of the phosphorane prepared from β-ionyl chloride with 3-methyl-2,4-hexadien-6-al-1-oic acid [92,93], followed by esterification. This condensation was carried out in dimethylformamide, and sodium acetylide or methoxide was used for the preparation of phosphorane. High yields of the final products were obtained.

An interesting new method has been suggested for the preparation of β-ionyltriphenylphosphonium chloride from β-ionol and triphenyl phosphine hydrochloride. The halide stage was thus by-passed. This method may also find application in the preparation of other phosphonium salts directly from alcohols.

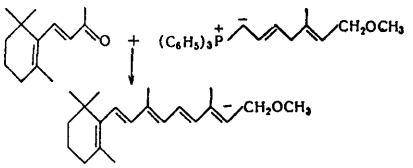
As already mentioned[30], ethoxycarbonylmethylenetriphenylphosphorane does not react with ketones. All efforts to condense ethoxycarbonylmethylenetriphenylphosphorane with nopinone have failed[94]. This factor limits somewhat the use of the Wittig reaction for the introduction of alkylideneethoxycarbonyl group.

The value of the Wittig reaction in isoprenoid chemistry is its wide applicability in the synthesis of various polyenyne hydrocarbons and acids otherwise difficult to obtain, and also because, by the selection of appropriate components, it can be used for the synthesis of their derivatives containing functional groups: alcohols, ethers, aldehydes, and ketones. These potentialities of the Wittig reaction have by no means been fully exploited yet, but they can be adequately assessed on the basis of available data.

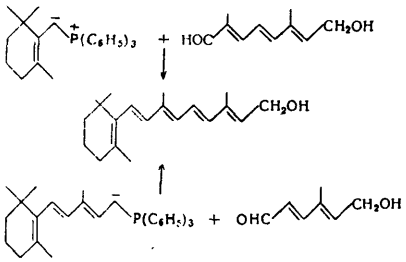
A number of patents[95-99] deals with simple new methods for the synthesis of vitamin A, its ethers, and 11,12-dehydrovitamin A. In one of these[85,95], the easily obtained β-ionylideneacetic aldehyde is condensed with 2-methyl-4-methoxy-2-butenylidenetriphenylphosphorane directly to give the methyl ether of vitamin A:



In another method[96,98] the vitamin A methyl ether is prepared by the reaction of β-ionone with 1-methoxy-3-methyl-2,4-hexadienylidenetriphenylphosphorane:



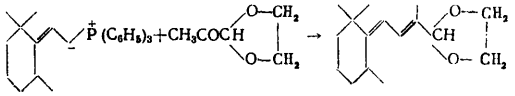
Vitamin A itself was obtained by the condensation of β-cyclogeranylidenetriphenylphosphorane[97] with 8-hydroxy-2,6-dimethyl-2,4,6-octatrien-1-al, or of β-ionylideneethylidenetriphenylphosphorane[88,89] with 6-hydroxy-4-methyl-2,4-hexadien-1-al:



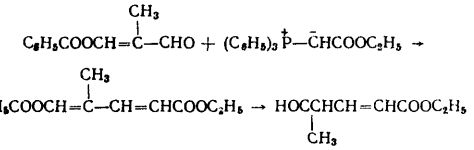
In the foregoing reactions, hydrocarbon phosphoranes and hydroxyaldehydes were used. The application of alkoxyaldehydes or acetoxyaldehydes leads in this case to the formation of ethers or the acetate derived from vitamin A.

The above methods compete with the one at present used for the industrial manufacture of vitamin A.

The introduction of an aldehyde group using the Wittig reaction has not yet been sufficiently developed. One of the patents by Isler and collaborators[100] describes the interesting condensation of 2-(2′,6′,6′-trimethylcyclohexylidene)ethylidenetriphenylphosphorane with 2-oxopropanal-1-ethyleneacetal, which yields the ethyleneacetal of the corresponding aldehyde:

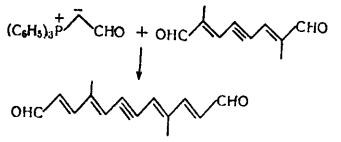


The introduction of an aldehyde group by means of the Wittig reaction can also be carried out by using enolic esters of dialdehydes. For example, it was reported[30] that ethoxycarbonylmethylenetriphenylphosphorane reacts with methylmalonic dialdehyde benzoate to form the corresponding enolic ester of an aldehydic carboxylic acid, which after saponification yields the corresponding aldehydic acid.



This is a simple and convenient method for the preparation of difunctional derivatives.

Trippett and Walker[31] (see section 2) have recently suggested the use of formylmethylenetriphenylphosphorane for the introduction of aldehyde groups. This phosphorane reacts with 2,7-dimethyl-2,6-octadien-4-yne-1,8-dial forming 4,9-dimethyl-2,4,8,10-dodecatetraen-6-yne-1,12-dial, a valuable intermediate in the synthesis of carotenoids:



The yield of the final dialdehyde was 50% according to spectral data, but owing to difficulties involved in its separation from the large quantity of triphenylphosphine, it was isolated in only 15% yield.

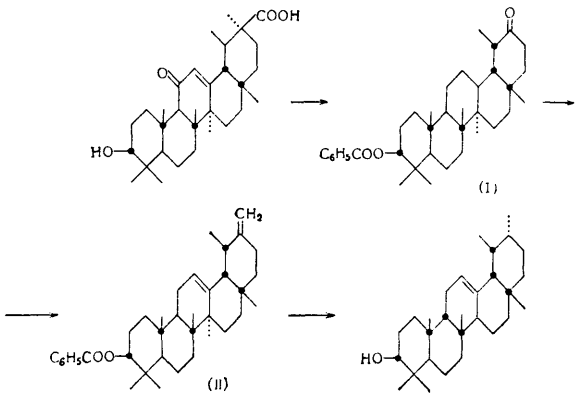
In the next section we shall discuss in detail another possible method of introducing an aldehyde group by means of methoxymethylenephosphorane[45].

The introduction of a keto group using the Wittig reaction can be carried out with acetylmethylenephosphorane, as was first reported by Ramirez[29]. This method, however, has hardly been used. An interesting new method[35] for the synthesis of γ-bromoacids has appeared recently:

$$CH_3CHBrCHO + (C_6H_5)_3P{=}CHCOOC_2H_5 \rightarrow CH_3CHBrCH{=}CHCOOC_2H_5 .$$

We conclude this section by mentioning the work by Corey and Cantrall[101] on the stereochemical relationships in the triterpenic series. They treated glycyrrhetic acid (a β-amyrin derivative of known configuration) with a

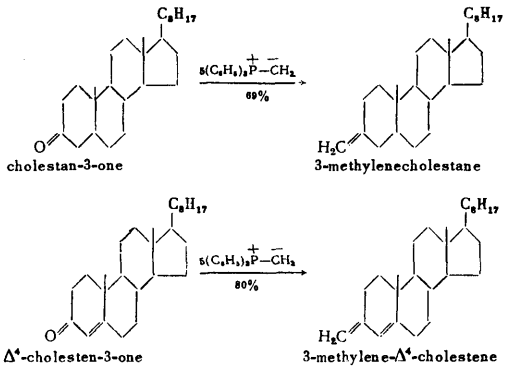
Wittig reagent and obtained, *via* ketone (I), an olefine (II), whose selective reduction by lithium in diethylamine gave α-amyrin.



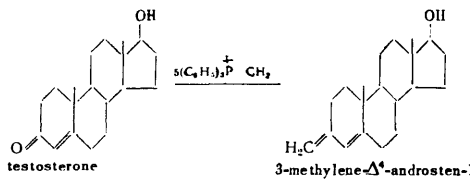
6. SYNTHESIS OF STEROIDS AND VITAMIN D_2

Barton *et al.*[102] were the first to use the Wittig reaction in the steroid series, in their synthesis of 3-methylcholestan-3-one. Since 1957 this reaction has been widely applied to the steroid series, and its importance in that field is likely to increase. So far, it has only been used for the introduction of a methylene group.

Sondheimer and Mechoulam[103,104] made a thorough study of the introduction of a methylene group by means of the Wittig reaction. They became interested in this reaction while searching for a method for synthesising the side-chain in 17- and 20-ketosteroids. On boiling in tetrahydrofuran both saturated (cholestan-3-one) and unsaturated (Δ^4-cholesten-3-one) steroid ketones react readily with methylenetriphenylphosphorane forming the corresponding methylenesteroids of high purity, which are otherwise difficult to obtain.



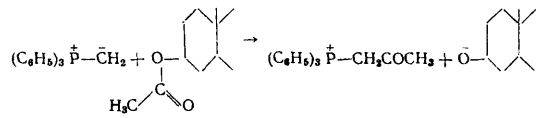
Steroid hydroxyketones react in the same way, and no screening of the hydroxyl group is necessary. For instance, testosterone reacts readily with methylenetriphenylphosphorane forming 3-methylene-Δ^4-androsten-17-ol in 75% yield.



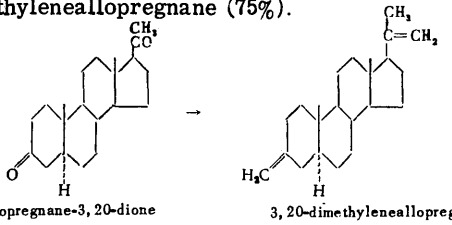
The reversibility of the first stage of the Wittig reaction (see section 3) is pronounced in the steroid series. A considerable excess of methylenetriphenylphosphorane should therefore be used in order to achieve maximum yields of methylenesteroids. For instance, the reaction of androstan-3β-ol-17-one[103] with three equivalents of methylenetriphenylphosphorane yields 32% of 17-methyleneandrostan-3β-ol, whereas by using five equivalents of the Wittig reagent a 58% yield is obtained. This also applies to the introduction of a methylene group into androstan-17β-ol-3--one, Δ^3-pregnen-3β-ol-20-one,[103] and allopregnan-3β-ol--20-one.[104]

Although protection of the hydroxyl group during the reaction is not strictly necessary, it does as a rule lead to higher yields. For instance, the introduction by the Wittig reaction of a methylene group into Δ^5-androsten-3β--ol-17-one yields 36% 17-methylene-Δ^5-androsten-3β-ol, while by using the corresponding tetrahydropyranyl ether the yield of the final product (after saponification) reaches 44%.[103]

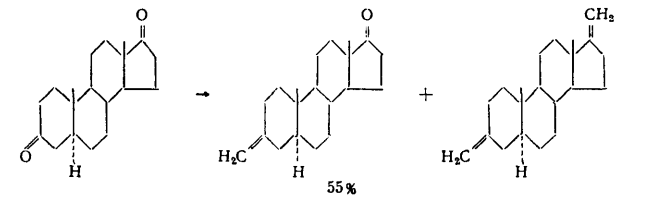
21-Nor-20-ketocholesterol and $\Delta^{5,16}$-pregnadien-3β-ol--20-one acetates, and androstan-3β,17β-diol-7-one and Δ^5-androsten-3β,17β-diol-7-one diacetates react with methylenetriphenylphosphorane without elimination of the acetate group[103,104]. In some cases, however, as in the reaction of hecogenin[102] or 7-ketocholesterol acetate[103], an acetyl group is eliminated, yielding 12-methylenetigogenin and 7-methylenecholesterol, respectively. The cleavage proceeds by the following general scheme:



Depending on their nature, steroid diketones may react once or twice. For instance, the reaction of methylenetriphenylphosphorane with allopregnan-3,20-dione[104] in ether solution at room temperature yields immediately 3,20-dimethyleneallopregnane (75%).



Under the same conditions androstan-3,17-dione[104] forms 3-methyleneandrostan-17-one as main product, and 3,17-dimethyleneandrostane as side-product.



Under identical conditions 3-methyleneandrostan-17-one gave 3,17-dimethyleneandrostane in 76% yield.

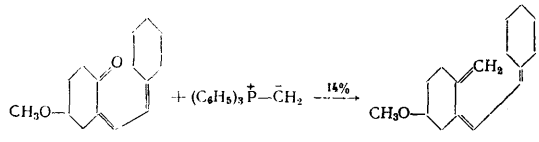
In addition to the above reactions, the introduction of the methylene group by Wittig's method has been used for the

synthesis of 24-methylenecholesterol[105,106] (contained in certain molluscs) and 25-dehydrocholesterol[107]. The condensation of 3β-acetoxy-5-cholenaldehyde with isopropylidenetriphenylphosphorane gave 24-dehydrocholesterol[108] identical with desmosterol, isolated from chick embryo.

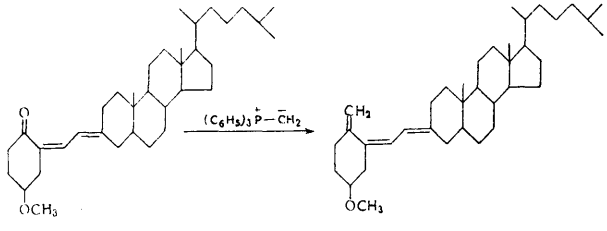
The fact that in the steroid series the Wittig reaction has been used almost exclusively for the introduction of methylene groups into ketosteroids is of no small significance since other methods are far less convenient, efficient or practicable.

The Wittig reaction can also be used for introducing groups other than methylene into steroids. For example, Levine[45] reacted tigogenone (5α,22β,25*D*-spirostan-3-one) with methoxymethylenetriphenylphosphorane and obtained 85% 3-methoxymethylene-5α,22β,25*D*-spirostane, which after extraction with ether saturated with 72% perchloric acid formed quantitatively 3-formyl-5α,22β,25*D*-spirostane. This method of introducing an aldehyde group, which was simultaneously suggested by Wittig[109], is undoubtedly very promising.

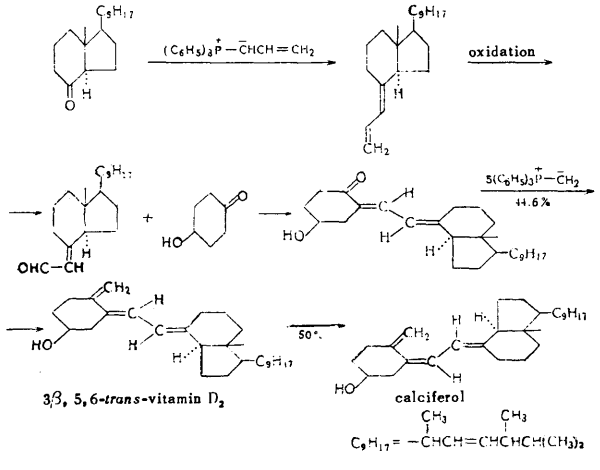
The possible contribution of the Wittig reaction to the synthesis of vitamin D_2 is of great importance. The classical experiments of Milas and collaborators[110,111] indicated the possibility of synthesising a system of double bonds typical of calciferol:



1-Cholestanylidene-2-(5′-methoxy-2′-methylenecyclohexylidene)ethane, the biologically active homologue of vitamin D_2, was synthesised according to that scheme[112].

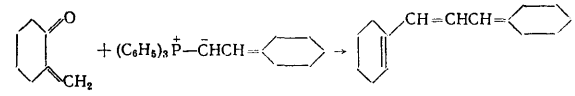


Finally, as a result of a systematic study, Inhoffen and collaborators[36,113-121] synthesised completely 3β-5,6-*trans*-vitamin D_2,[119-121] photoisomerisation of which yielded vitamin D_2 (calciferol):



This synthesis would have been impossible had the Wittig reaction not enabled the key-step, *viz*. the introduction of a methylene group in position 10. Harrison and Lythgoe[51,122-125], simultaneously and independently developed a method for the synthesis of calciferol using the Wittig reaction.

It was noticed, in the course of investigations of the methods for the synthesis of vitamin D_2, that certain unsaturated ketones are able to react with phosphoranes in 1,4--addition. For instance:



The above are examples of the successful uses of the Wittig reaction in the chemistry of natural products.

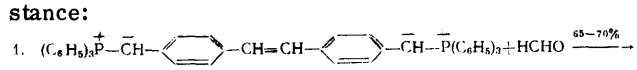
7. PROSPECTS FOR FUTURE USES OF THE WITTIG REACTION IN THE SYNTHETIC FIELD

In this section we shall briefly consider several contributions of the Wittig reaction other than the ones already discussed, and the prospects of its future development.

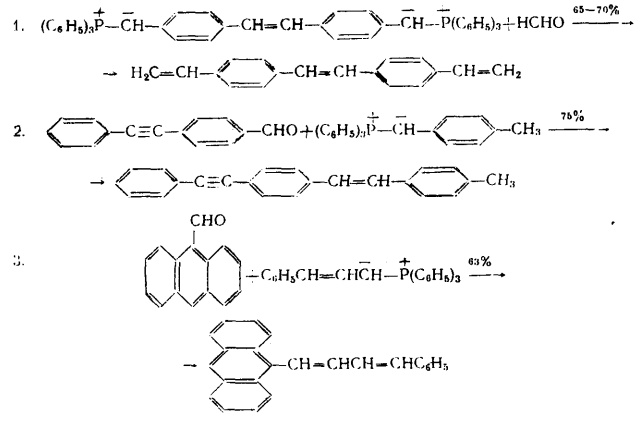
The Wittig reaction can of course be used not only in the synthesis of complex natural products, but also for numerous other materials. For the preparation of simple compounds, however, there is usually a wide choice of simpler methods, and the use of the Wittig reaction in such cases is unprofitable (*e.g.* the preparation of styrene from benzaldehyde and methylenetriphenylphosphorane, of 1-phenylbutadiene from cinnamic aldehyde and methylenetriphenylphosphorane, etc.). That is why the application of the Wittig reaction in organic synthesis is limited to complex natural compounds and related materials.

We shall now discuss the most interesting and promising applications of this reaction in organic synthesis.

Synthesis of hydrocarbons. The Wittig reaction can be used for the synthesis of a number of aliphatic and cyclic hydrocarbons which are difficult to prepare by the normal methods. For instance, the following synthesis of 3-pentadecen-1-yne[126] is attractive:

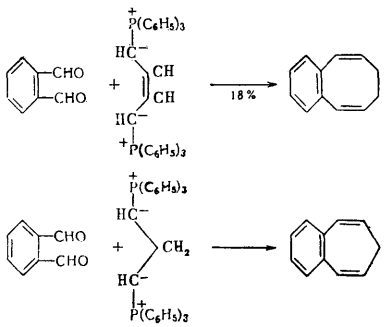


Drefahl and collaborators[127-129] used the Wittig reaction to prepare vinyl derivatives of stilbene, tolan, and arylbutadienes which are otherwise difficult to obtain. For instance:



Wittig and Pommer[130] have patented the preparation of various arylpolyene hydrocarbons.

Most interesting is the synthesis of 1,2-benzo-1,3,7--cyclooctatriene and 1,2-benzo-1,3,6-cycloheptatriene according to the following scheme[10,32]:



The synthesis of *o*-divinylbenzene[32] from *o*-phthalic dialdehyde and methylenetriphenylphosphorane in 75% yield may also have preparative importance, as may the synthesis of 9-vinylanthracene from 9-anthranyl aldehyde and methylenetriphenylphosphorane[131]. The Wittig reaction also proved useful in the preparation of 2-methoxy-3--methylstilbene[132].

As applied to aromatic ketones this reaction has significance only in special cases, for instance, in the synthesis of *o,o'*-distyrylbiphenyl[133], which cannot be prepared by the dehydration of the glycol obtained by the Grignard reaction of *o,o'*-dibenzoylbiphenyl and methylmagnesium bromide, since all attempts at dehydration result in cyclisation.

The reaction of alkylidenetriphenylphosphoranes with unsaturated ketones often consists in 1,4-addition. For instance, the synthesis of cross-conjugated hydrocarbons by the following scheme[40]:

$$C_6H_5(CH{=}CH)_n CO(CH{=}CH)_m C_6H_5 + (C_6H_5)_3\overset{+}{P}{-}\bar{C}H(CH{=}CH)_k C_6H_5$$

$n = 1 \quad m = 0 \quad k = 0,1$
$n = 2 \quad m = 1$
$n = 2 \quad m = 2$
$n = 2 \quad m = 0$

$$C_6H_5(CH{=}CH)_n C(CH{=}CH)_m C_6H_5$$
$$\|$$
$$CH(CH{=}CH)_k C_6H_5$$

In cases where $n = 0$, $m = 2$, and $k = 1$, in addition to normal reaction products, the product of 1,4-addition, *viz.* 1,6-diphenyl-1,3,5-hexatriene was also obtained. In other cases normal reaction products were obtained in high yields.

Synthesis of alkenyl halides. Another interesting extension of the Wittig reaction was discovered recently: the reaction of chlorocarbene with triphenylphosphine forming chloromethylenetriphenylphosphorane[134], which reacts with carbonyl compounds in the usual way:

$$(C_6H_5)_3P + :CHCl \rightarrow (C_6H_5)_3\overset{+}{P}{-}\bar{C}HCl \xrightarrow[31\%]{(C_6H_5)_2CO}$$
$$\rightarrow (C_6H_5)_2C{=}CHCl + (C_6H_5)_3PO.$$

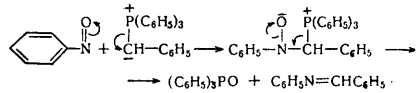
The reaction with dichlorocarbene proceeds likewise[135]:

$$(C_6H_5)_3P + :CCl_2 \rightarrow (C_6H_5)_3\overset{+}{P}{-}\bar{C}Cl_2 \xrightarrow[40\%]{(C_6H_5)_2CO}$$
$$\rightarrow (C_6H_5)_2C{=}CCl_2 + (C_6H_5)_3PO.$$

These are the new methods for the preparation of 1-mono- and 1,1-di-haloolefines.

Synthesis of acids. According to Bohlmann[44] the preparation of methyl esters of 5-arylsorbic acids by the reaction of substituted benzaldehydes with methoxycarbonylvinylmethylenetriphenylphosphorane, in the case of nitro-, chloro-, and hydroxy-benzaldehydes, is preferred to the Reformatski reaction between substituted benzaldehydes and the methyl ester of γ-bromocrotonic acid.

Reaction with nitroso compounds. It was established[10,136] that nitroso compounds, where the nitroso group, like the carbonyl group, has an electrophilic character, can combine with alkylidenetriphenylphosphoranes to form Schiff's bases:



Since Schiff's bases readily hydrolyse to carbonyl compounds, this reaction is a new method for the preparation of aldehydes and ketones. For instance, the reaction of geranylidenetriphenylphosphorane with nitrosobenzene gave good yield of citrylidene anil, which on hydrolysis yielded citral[10]. Similarly, fluorenylidenetriphenylphosphorane and nitrobenzene gave fluorenylidene anil[136].

Reaction with isocyanates. Staudinger and Meyer[1] described the reaction of diphenylmethylenetriphenylphosphorane with phenylisocyanate to form diphenylketene phenylimine:

$$(C_6H_5)_3\overset{+}{P}{-}\bar{C}(C_6H_5)_2 + O{=}C{=}N{-}C_6H_5 \rightarrow (C_6H_5)_2C{=}C{=}NC_6H_5.$$

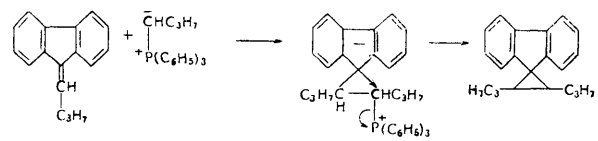
Reaction with ketens. According to Lüscher (see Meyer[137,138]) diphenylmethylenetriphenylphosphorane reacts with diphenylketen according to the scheme:

$$(C_6H_5)_3\overset{+}{P}{-}\bar{C}(C_6H_5)_2 + O{=}C{=}C(C_6H_5)_2 \xrightarrow{140^\circ}$$
$$\rightarrow (C_6H_5)_2C{=}C{=}C(C_6H_5)_2 + (C_6H_5)_3PO.$$

Reaction with thiocarbonyl compounds. Thiobenzophenone and Michler thioketone react with methylenetriphenylphosphorane like ordinary ketones[10]:

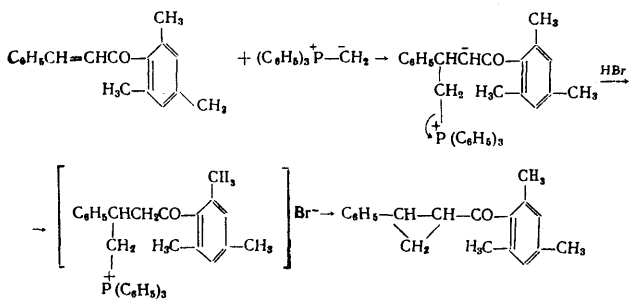
$$R_2CS + H_2\bar{C}{-}\overset{+}{P}(C_6H_5)_3 \rightarrow (C_6H_5)_3PS + R_2C{=}CH_2$$
where $R = C_6H_5$, or p-$(CH_3)_2NC_6H_4$.

Addition of alkylidenephosphoranes to a double bond. Alkylidenetriphenylphosphoranes react with readily polarisable C–C bonds. For example, propylmethylenetriphenylphosphorane reacts with 9-n-butylidenefluorene according to the scheme[139]:



Alkylidenetriphenylphosphoranes can thus be used for the synthesis of the cyclopropane ring. Freeman[140] showed that methylenetriphenylphosphorane unites with the double

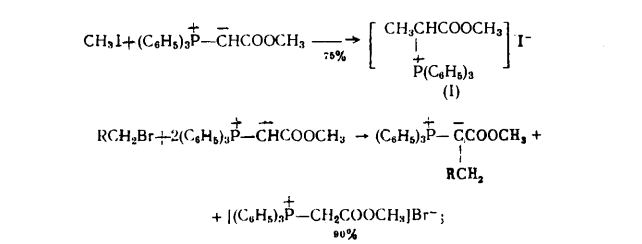
bond of mesityl styryl ketone forming a product which with hydrogen bromide yields an insoluble, unstable phosphonium salt:



Heating this salt in xylene solution for four hours results in the formation of 2-phenylcyclopropyl mesityl ketone in 52% yield.

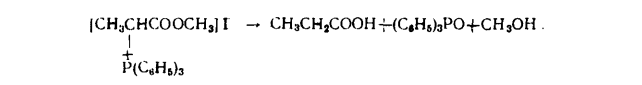
The formation of tribenzoylcyclopropane (in but 7% yield) was recently observed in the reaction of benzoylmethylenetriphenylphosphorane with phenacyl bromide[141].

Bestman[142,143] described recently a very promising addition reaction of alkylidenetriphenylphosphoranes. He showed that in boiling ethyl acetate solution methyl iodide as well as α-bromoacids react with the double bond in methoxycarbonylmethylenetriphenylphosphorane according to the scheme:



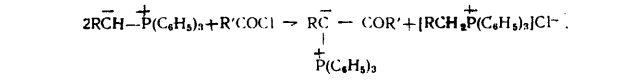
for (II) R = $COOCH_3$ (75%); for (III) R = C_6H_5 (80%).

Upon alkaline hydrolysis (I) decomposes to acid, triphenylphosphine, and methanol:



II and III decompose under the same conditions forming succinic and hydrocinnamic acid respectively, in 90–100% yield. This is a new method for the synthesis of mono- and di-carboxylic acids.

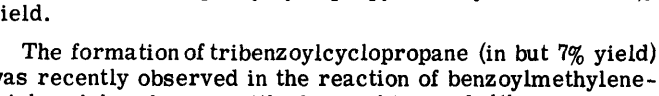
Acid chlorides were found to be capable of analogous addition reactions[143].



The yield of acetylalkylidenetriphenylphosphorane is 60–80%. When R = C_6H_5, the resulting products were stable to hydrolysis, while the alkyl derivatives hydrolyse forming ketones. This is a new method for the preparation of ketones from acid chlorides and alkylidenetriphenylphosphoranes.

Auto-oxidation. Bestman[144] observed the formation of symmetrical olefines from alkylidenetriphenylphosphoranes as a result of auto-oxidation. Auto-oxidation of benzylidenetriphenylphosphorane yields 55% stilbene (35% *trans*- and 20% *cis*-form); similarly cinnamylidenetriphenylphosphorane yields 1,6-diphenylhexatriene. This reaction proceeds via the formation of an aldehyde which subsequently condenses with the excess of phosphorane:

Reaction with $LiAlH_4$. In the reaction of lithium aluminium hydride with alkylidenetriphenylphosphoranes in tetrahydrofuran at -20°, hydrogen adds on to the carbon in the methylene group and a phenyl group is split off from the phosphorus atom[145]:



Yields are not higher than 34–42%.

Reaction with metal salts. Seyferth[146,147] recently studied the reaction of methylenetriphenylphosphorane with the halides of the metals from groups II, IV, and V of the Periodic Table. This reaction results in the formation of phosphonium salts soluble in water. For instance, methylenetriphenylphosphorane and mercuric bromide gave a salt of the composition $[(C_6H_5)_3PCH_2HgCH_2P.(C_6H_5)_3][HgBr_3]_2$; under the same conditions trimethylbromosilane forms $[(C_6H_5)_3PCH_2Si(CH_3)_3]Br$, and dimethyldibromostannane forms $[(C_6H_5)_3PCH_2Sn(CH_3)_2CH_2P(C_6H_5)_3].[(CH_3)_2SnBr_4]$.

The above examples illustrate the trends in the further development of the Wittig reaction and its application in organic synthesis.

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VIBRATIONAL SPECTRA OF ORGANOPHOSPHORUS COMPOUNDS

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I. INTRODUCTION

At the present time organophosphorus compounds are being intensively studied. This fact is related to their great theoretical importance and to their various applications in industry and agriculture. They have been used for some time as flotation agents, plasticisers, additives for lubricating oil, etc. Since many organophosphorus compounds exhibit a specific physiological activity, their use as medical preparations is becoming more and more widespread. In recent years they have been widely used for chemical crop protection. Various phosphorothioates have proved particularly valuable, being considerably more effective than many previously known insecticides. The prospects in the development of the chemistry of organic phosphorus compounds, including polymers, are very good. The possibilities of practical utilisation of these compounds are far from exhausted and in some fields their application is only beginning.

In the synthesis of new organophosphorus compounds many problems arise in establishing their structure and studying their reactions. In particular, the study of tautomerism, isomerism, and molecular rearrangements in a series of organophosphorus compounds is of great theoretical and practical interest to organic chemistry. A wide range of physical and chemical methods is necessary to solve these and other problems. Among the physical methods, vibrational spectra are very important.

Many investigations have been reported of the vibrational spectra of organophosphorus compounds, mainly in recent years. In some of these, mostly qualitative in character, the spectra of compounds of known structure are analysed and the observed frequencies are assigned to the vibrations of individual bonds or groups of bonds. Many of these assignments have been made by comparison of the spectra of a large number of compounds and are well established; others are insufficiently well founded and cannot always be recommended for use in structure determination. In a number of publications on the vibrational spectra of organophosphorus compounds attempts are made to explain shifts in the so-called characteristic frequencies, when comparing the spectra of certain compounds with those of others. As a rule, the frequency shifts are ascribed to the influence of some particular factor, *e.g.* polarity of bonds, mass of atoms, etc.

Experimentally and theoretically it is well known that the characteristic vibration frequencies of bonds can change considerably when the intramolecular environment of the bonds to which these frequencies are assigned is changed. The reasons for changes in characteristic frequencies, even if one considers only isolated molecules, can be very varied.