THE SYNTHESIS AND REACTIONS OF ENOL-LACTONES

SOME SKELETAL REARRANGEMENT PROCESSES OF PHOSPHORANES UPON ELECTRON IMPACT

A THESIS PRESENTED

for the

DEGREE OF MASTER OF SCIENCE

in the

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by

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CONTENTS

STATEMENT

The work described in this thesis incorporates no material previously submitted for a degree an any University, except where due reference has been made.

A. G A R A

PUBLICATIONS

Some of the work described in this thesis has been published in the following papers:

1. A Synthesis of Enol Lactones.
   A.P. Gara, R.A. Massy-Westropp and G.D. Reynolds.
   Tetrahedron Letters, 1969, 4171.

2. Some Skeletal Rearrangement Processes of Phosphoranes upon Electron Impact.
   A.P. Gara, R.A. Massy-Westropp and J.H. Bowie.
   Aust.J.Chem., 1970, 23, 307.

ACKNOWLEDGEMENTS

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I would also like to thank Mr. T. Blumenthal and Dr. J.H. Bowie for the determination and interpretation of the mass spectra.

This research was carried out during the tenure of a Commonwealth Postgraduate Award, which I gratefully acknowledge.

SUMMARY

The Wittig reaction between cyclic, five-membered, aliphatic anhydrides and stable unreactive phosphoranes leads to a convenient preparation of enol-lactones. The reaction was first investigated by Reynolds and his results have been extended in this study. It is a general reaction with good yields, and all anhydrides, except maleic, have yielded the expected enol-lactones. Although most of the work has been carried out with methylcarbonylmethylidene triphenyl-phosphorane and ethoxycarbonylmethylidene triphenyl-phosphorane, eight different phosphorus ylids have been used successfully. A mechanism has been suggested and it is proposed that dipolar repulsion in the intermediate betaine is the most important factor to be considered in predicting the stereochemistry of the product.

Enol-lactones prepared from succinic anhydride, having no double bond in the ring, react readily with urea and thiourea in the presence of sodium ethoxide to give the corresponding pyrimidines. Other but-2-ene-4-olides react with sodium ethoxide in the presence or absence of urea and yield acylcyclopent-4-ene-1,3-diones. A mechanism has been proposed for both reactions.

Attempts to prepare *cis*- and *trans*-4-(2-chloro-

propylidene)-2-methylbut-2-ene-4-olide and the corresponding phosphonium salts have been unsuccessful.

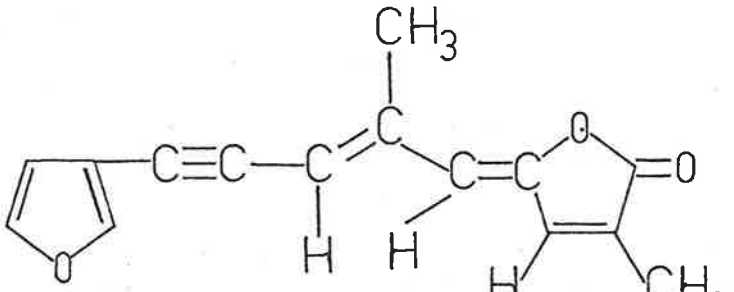
The mass spectra of acyl phosphoranes exhibit peaks which arise by P-O bond formation. The problem of thermal against electron impact rearrangement is considered and the rearrangements have been studied by deuterium labelling. The formation of the fluorenyl cation (m/e 165) has also been investigated.

PART I

A: THE SYNTHESIS OF ENOL-LACTONES

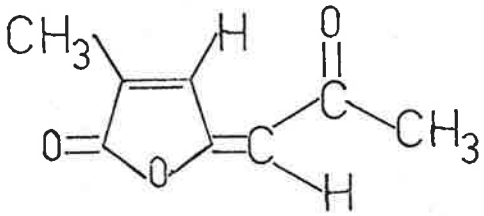
INTRODUCTION

Freelingyne (1), a β-substituted furano sesquiterpene, was isolated from the wood oil of *Eremophila freelingii* and the structure (1) was proposed by Reynolds.[1]



(1)

Reynolds[2] synthesized the key intermediates, γ-(3-furyl)propargyl bromide (4) and the *cis* and *trans* 4-methylcarbonylmethylidene-2-methylbut-2-ene-4-olide (2) and (3).



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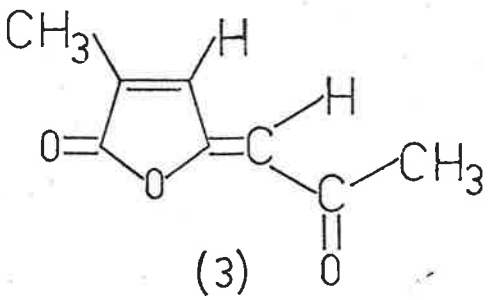

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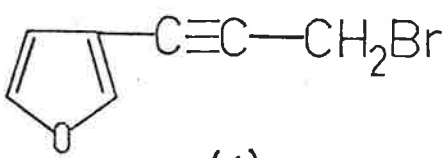
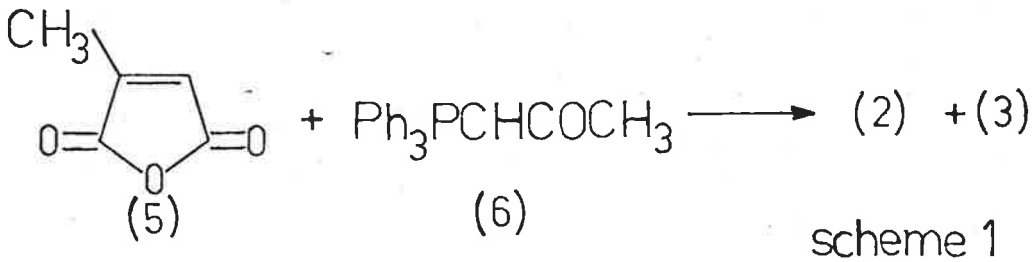


(4)

The bromide (4) was prepared from 3-furoic acid and the enol-lactones (2) and (3) by direct reaction of

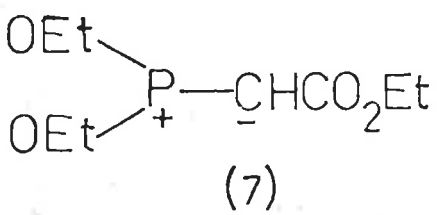
citraconic anhydride (5) and methylcarbonylmethylidene triphenylphosphorane (6) (scheme 1).

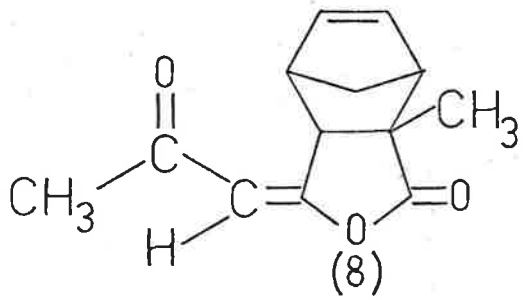


scheme 1

This method, analogous to that developed by Chopard,[3] was preferred over other methods of preparation of enol-lactones[4,5] which involved base catalysed cyclisation of acetylenic acids.

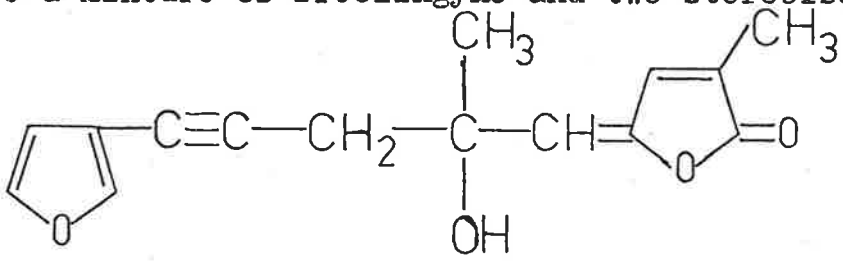
The proposed direct synthesis of freelingyne via a Wittig reaction between the enol-lactones (2) and (3) and the reactive phosphorane derived from the bromide (4) was unsuccessful. The failure was attributed to the unreactivity of the carbonyl group in the enol-lactone. This was confirmed by the fact that the reactive phosphonate anion, diethylethoxycarbonylmethylphosphonate (7), did not react with the enol-lactones (2), (3) or the Diels Alder adduct (8) even at elevated temperatures.[6]





Reynolds[2] synthesized freelingyne by converting the bromide (4) to a metal alkyl followed by treatment with

the enol-lactones (2) or (3). The alcohol (9), which retained the stereochemistry exocyclic to the lactone ring, was dehydrated with phosphorus oxychloride in pyridine to give a mixture of freelingyne and two stereoisomers.



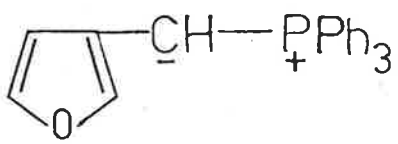
(9)

The current investigation began in an attempt to develop an efficient method for the stereospecific synthesis of freelingyne (1). The work carried out by Chopard[3] on phthalic anhydride and particularly Reynolds[2] who investigated the Wittig reaction between stable phosphoranes and cyclic, five-membered, aliphatic anhydrides prompted further work into the utility of this reaction. Various schemes are available for the stereospecific synthesis of freelingyne using a Wittig reaction.

(a) Treatment of the reactive ylid derived from the bromide (10) with citraconic anhydride (5).

(b) Treatment of the stable ylid derived from the bromide (11) with citraconic anhydride (5) and subsequent Wittig reaction with the reactive ylid (12) should provide a method of synthesizing the dihydro isomers of freelingyne, two of which occur naturally.

(c) Treatment of the reactive ylid derived from the acetal of the bromide (11) as in (b) above.



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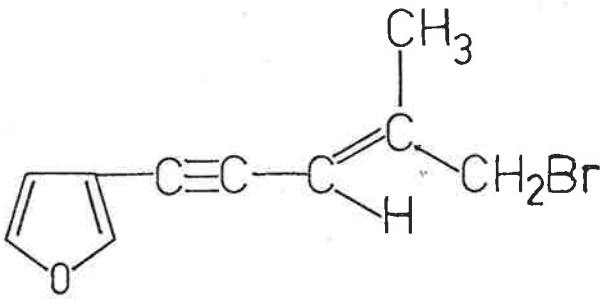

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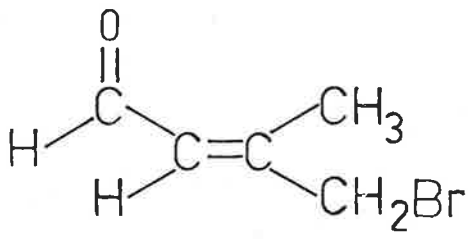


(11)

These methods depend on whether or not reactive ylids will react with anhydrides to yield enol-lactones. The failure of several reactive ylids and phosphonate anions to react with anhydrides[6,7,8] prompted an investigation into the mechanism of the Wittig reaction between stable ylids and anhydrides.

The stability of the phosphorane and the nature of the carbonyl compound have a direct effect on the mechanism and stereochemistry of the Wittig reaction. The accepted mechanism of the Wittig reaction between stable phosphoranes and carbonyl compounds, especially with respect to the stereochemistry of the products, will be discussed in order to determine whether this mechanism can be applied to the

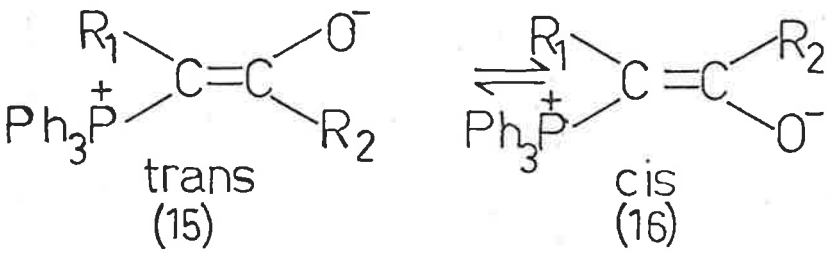
Wittig reaction of stable phosphoranes and anhydrides.

Alkylidene phosphoranes are considered as resonance hybrids of two limiting structures, the predominant ylid form (13) and the xylene form (14) which has been shown to be present by kinetic studies.[9]

(13) (14)

The reactivity of the phosphoranes is determined by the distribution of the negative charge in the molecule. Electron withdrawing groups R_1 and R_2 will stabilise the negative charge, decrease the nucleophilicity and thus reduce the activity of the phosphorane. The groups R on phosphorus also influence the reactivity of the phosphorane, but as the present study involves only triphenyl phosphoranes, this factor may be neglected.

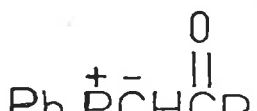
Recent work by Bestmann[10,11] has shown that a wide variety of ester stabilised phosphoranes (15) (R_2 = $O\overset{1}{\underset{\wedge}{}}$Alkyl) are best described by equilibrating forms (15) and (16),



trans (15) cis (16)

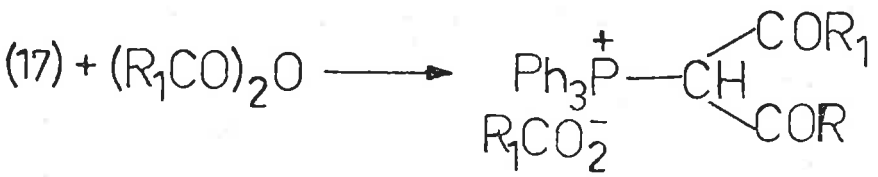
whereas carbonyl stabilised phosphoranes (15) (R_2 = alkyl) exhibit <u>cis</u> stereochemistry (16).

The unreactive phosphoranes, which are stable to hydrolysis, undergo the Wittig reaction with reactive carbonyl compounds such as benzaldehyde[12] and also ketones[13-16] under forcing conditions. Resonance stabilised ylids are not necessarily attacked on the α carbon atom. Acylmethylene triphenylphosphoranes are alkylated on oxygen[12] whereas methoxycarbonylmethylidene triphenylphosphorane is alkylated on carbon[17,18], when they are treated with alkyl halides. Studies[19-21] on the acylation reactions of acid chlorides with stable phosphoranes (17) indicate that the direction of acylation is determined by the nature of R.



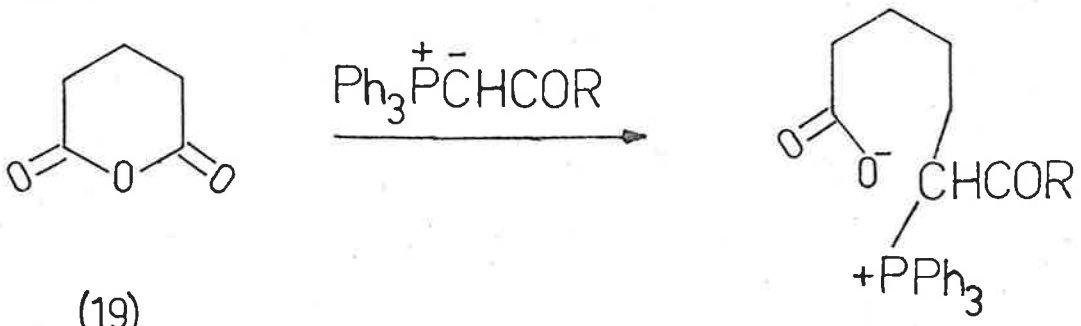
(17)

Chopard[22] studied the acylation of stable phosphoranes (17) with acid anhydrides and showed that the reaction took place at the carbon atom to yield the new phosphonium salt (18).



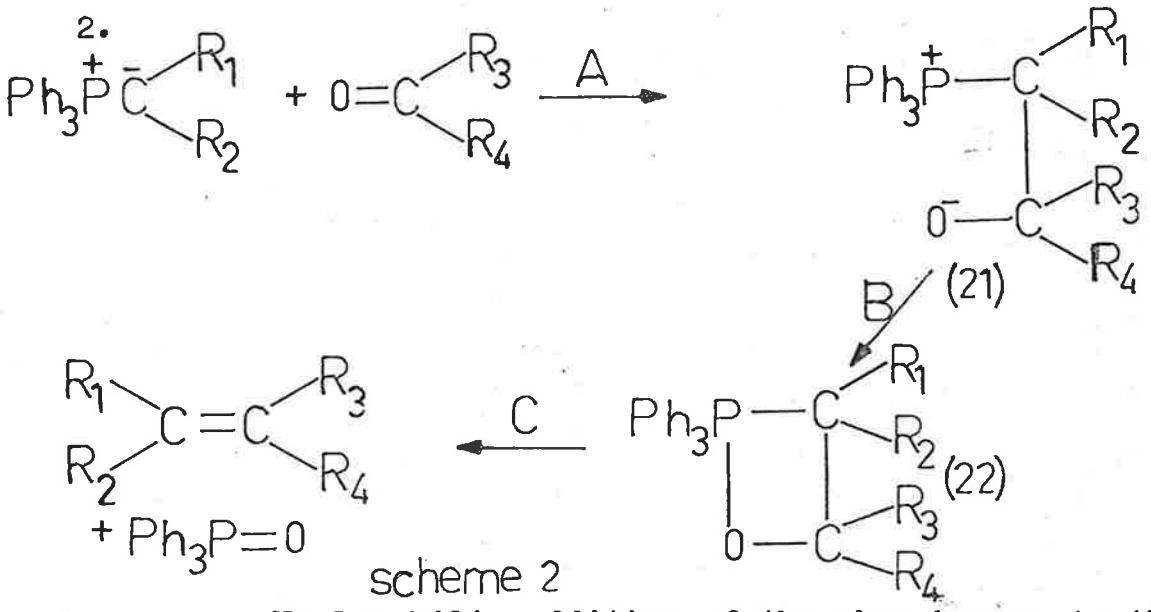
(18)

An analogous reaction was observed with the six-membered cyclic anhydride, glutaric anhydride (19) in which a good yield of the phosphonium salt (20) was obtained.



(19) (20)

Olefin formation from phosphoranes and carbonyl compounds occurs by way of the intermediates shown in scheme 2.



scheme 2

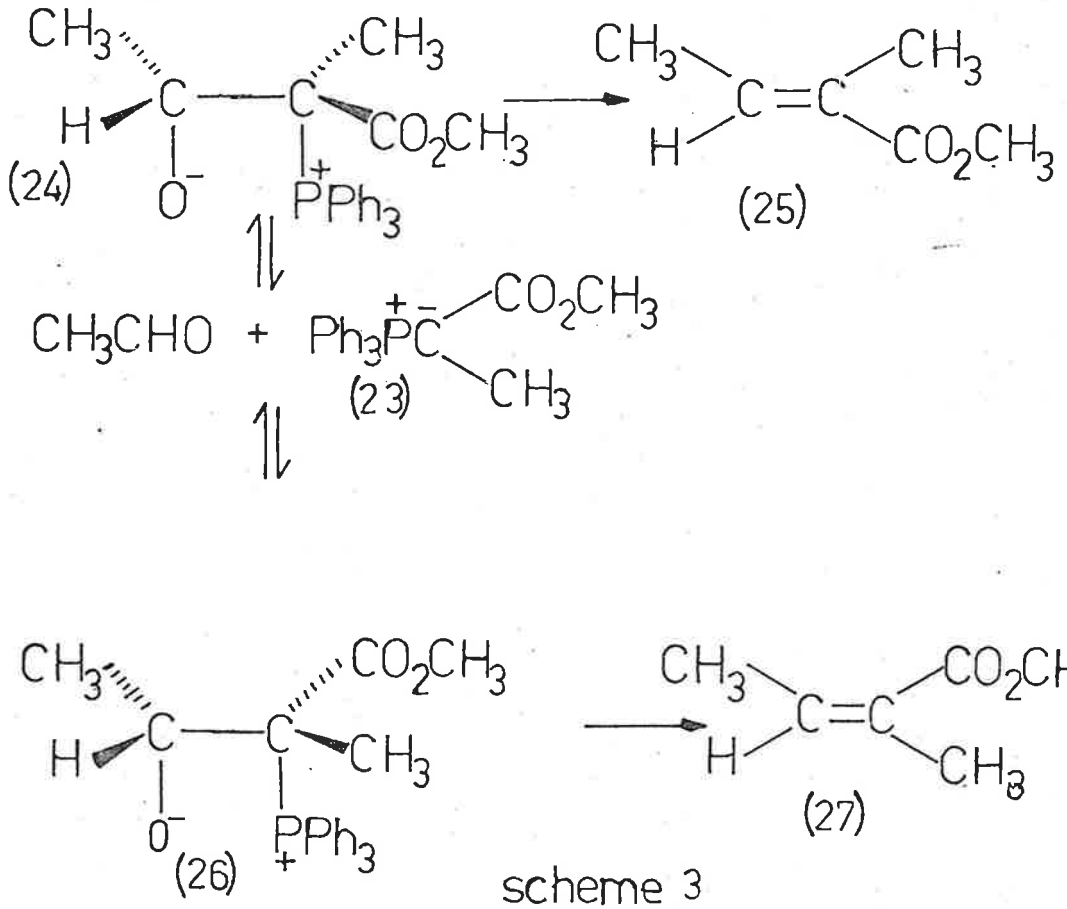
Nucleophilic addition of the phosphorane to the polarized carbonyl group gives the phosphonium betaine (21). As a consequence of the great affinity of phosphorus for oxygen and the possibility of expanding the valence shell of phosphorus to ten electrons, a P-O bond is formed giving rise to the four-membered ring compound (22) which then

collapses into triphenyl phosphine oxide and an olefin. Evidence has been obtained for the presence of the betaine[23] (21) when it was characterized as its hydrobromide. Since it has never been observed that step C is the slowest and, therefore, the rate determining step in a Wittig reaction, it cannot be decided whether the four-membered ring compound (22) with a pentavalent phosphorus atom is actually an intermediate or a transition state. Depending on the reactants, however, either step A or step B may become rate determining.

Kinetic studies[24-26] with resonance stabilized phosphoranes and a variety of aromatic aldehydes indicate that the overall reaction is best described as a slow reversible formation of the betaine (rate controlling) with rapid decomposition of the betaine into triphenyl phosphine oxide and an olefin. In the interaction of carbonyl compounds with reactive phosphoranes,[27] the addition of the ylid to the carbonyl group takes place within a few minutes whereas the subsequent decomposition of the betaine sometimes requires prolonged heating.

In the reaction between carbonyl compounds and phosphoranes a mixture of <u>cis</u> and <u>trans</u> olefins is usually obtained, but reviews[28-31] of the Wittig reaction indicate that it is possible to control the stereochemistry to a considerable degree. Corey[32] has shown that the reaction of pivalaldehyde with n-octylidene and β-phenylethylidene

triphenylphosphoranes gave cis olefins and these model reactions were applied in the syntheses of humulene[33] and the prostaglandins.[34] However, the trans isomer usually predominates in Wittig reactions if resonance stabilised phosphoranes are used. This is shown in the preparation of 2-methyl-2-butenoate[35] (scheme 3) from the stable ylid (23) and acetaldehyde resulting in the almost exclusive formation of methyl tiglate (25), the trans isomer.

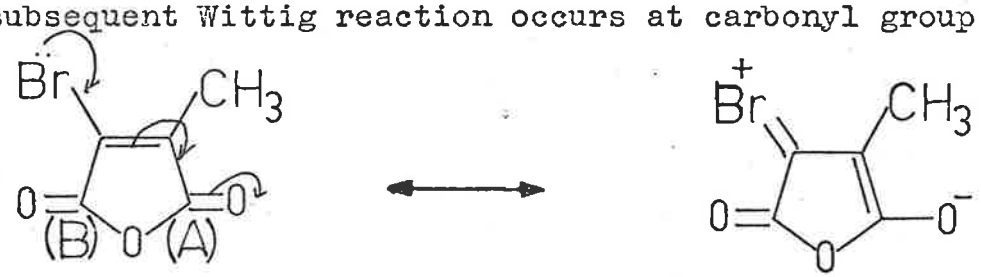


scheme 3

To rationalize the observed isomer distribution it is assumed that the resonance stabilised phosphorane (23) is in equilibrium with the two betaines (24) and (26).

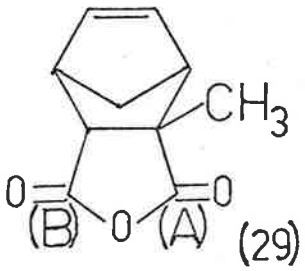
This slowest step is probably reversible so that the reaction may proceed predominantly by way of the betaine (24) of lower energy, which has a CH_3-CH_3 interaction rather than a CH_3-CO_2CH_3 interaction as in betaine (26), thus leading to the trans olefin (25).

However the predominance of cis olefins in the Wittig reaction between cyclic five-membered anhydrides and stable phosphoranes indicates that factors other than steric must be considered if the above mechanism is to be utilized. Both electron and steric factors in the anhydride must be considered in predicting the products of a Wittig reaction. In bromocitraconic anhydride[6] (28) the electron donating effect of the bromine deactivates carbonyl group (A) and subsequent Wittig reaction occurs at carbonyl group (B).



(28)

When citraconic anhydride (5) was treated with the phosphorane (6) (scheme 1) attack of the phosphorane occurred at both carbonyl groups.[2] Synthesis of the anhydride (29), by a Diels Alder reaction between citraconic anhydride and cyclopentadiene, placed carbonyl group (A) in a more stericly crowded position and subsequent Wittig reaction[2,6] took place at the less hindered carbonyl group (B).

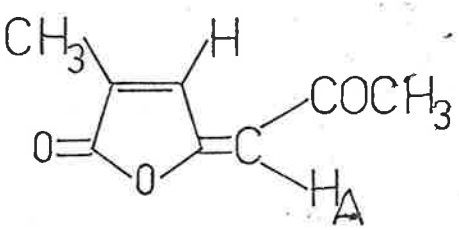


(29)

The above two examples indicate that steric and electronic factors in both the anhydride and the phosphorane must be considered in the mechanism of the Wittig reaction.

DISCUSSION

Treatment of cyclic five-membered aliphatic and aromatic anhydrides with resonance stabilised phosphoranes gave enol-lactones (e.g. cis and trans 4-methylcarbonyl-methylidene-2-methylbut-2-ene-4-olide (2) and (3)) whose stereochemistry was based on an analysis of the n.m.r. data.



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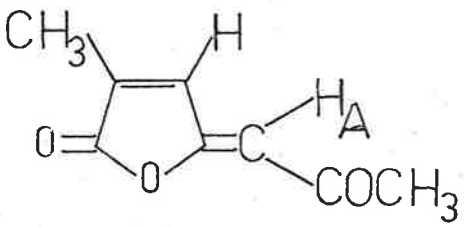
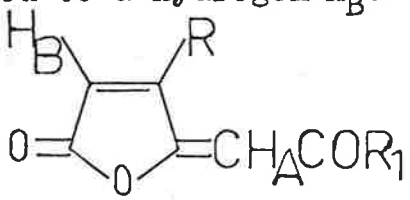


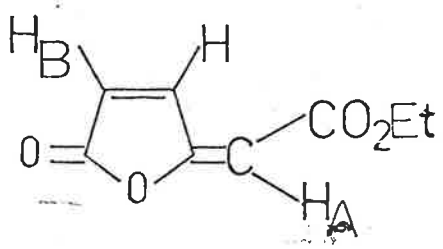
(3)

Proton H_A resonates at a lower field when it is in the trans orientation due to the deshielding of the proton by the ring oxygen of the lactone. From a study of the n.m.r. data[6] of enol-lactones, an absorption in the range 3.7 to 4.2 τ indicated formation of the cis enol-lactone and an absorption in the range 4.3 to 4.7 τ indicated the trans compound. The assignment of stereochemistry can be confirmed in those enol-lactones where H_A can be coupled to a hydrogen H_B.



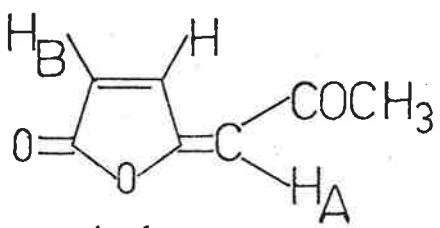
(30)

The coupling constant for the exovinyl hydrogen H_A and H_B is larger in cis enol-lactones than in trans enol-lactones. In the enol-lactone (31) previously proposed as cis on the basis of the absorption of proton H_A the coupling constant between H_A and H_B is 1.9Hz.

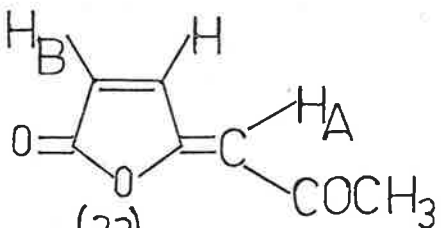


(31)

A similar coupling constant has been observed by Fowler and Seltzer[36] who prepared the cis and trans enol-lactones (32) and (33).



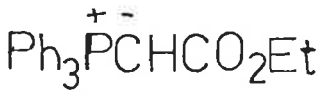
(32) $J_{AB} = 1.8Hz$



(33) $J_{AB} = 0.8Hz$

The Wittig reaction between phosphoranes and anhydrides is a general reaction with good yields (see Table 1) and although most of the work has been carried out with ethoxycarbonylmethylidene triphenylphosphorane

(34) and methylcarbonylmethylidene triphenylphosphorane (6) eight different phosphorus ylids have been used successfully.



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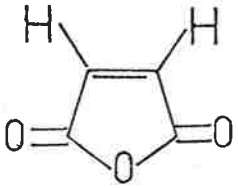
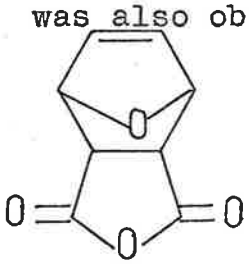


(35)

Citraconic, dimethylmaleic, succinic, phthalic and various substituted succinic and maleic anhydrides have all yielded the expected enol-lactones. The reaction failed with maleic anhydride (35) probably due to an addition of the nucleophilic phosphorane across the activated double bond of the anhydride. Such Michael type additions of phosphoranes to activated double bonds have been observed,[37] particularly if the phosphorane is resonance stabilised. However, this problem was overcome by using the Diels-Alder adduct with furan (36). The product (37) underwent a facile retro Diels-Alder reaction to give the desired enol-lactone (38). A low yield of the <u>cis</u> Diels Alder enol-lactone (37) was <u>also</u> obtained.



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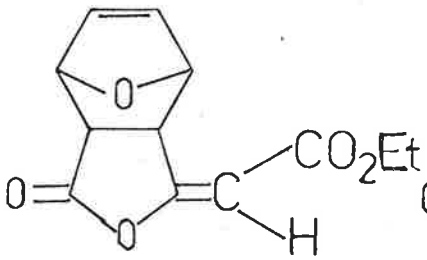

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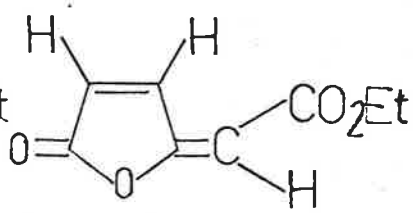


(38)

The results obtained in the Wittig reaction between anhydrides and stabilised phosphoranes are summarised in Table 1. The results obtained by Reynolds[2] are also included for the purpose of comparing the stereochemistry of all the enol-lactones prepared in this reaction.

TABLE 1

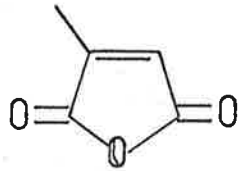
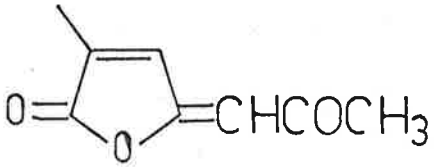
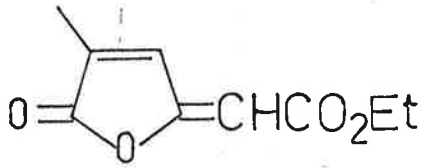
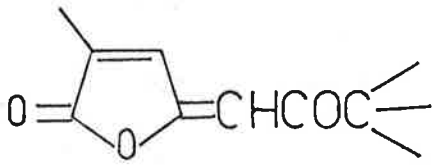
ANHYDRIDE	YLID	PRODUCT	% cis	% trans.
 (5)	$Ph_3\overset{+}{P}\overset{-}{C}HCOCH_3$ (6)	 (2)+(3)	24	22
(5)	$Ph_3\overset{+}{P}\overset{-}{C}HCO_2Et$ (34)	 (39)+(40)	(60)	1
(5)	$Ph_3\overset{+}{P}\overset{-}{C}HCOC$ (41)	 (42)	13	-

TABLE 1 cont.

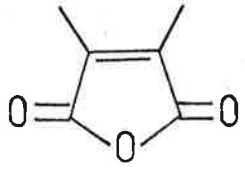
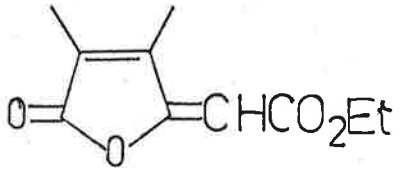
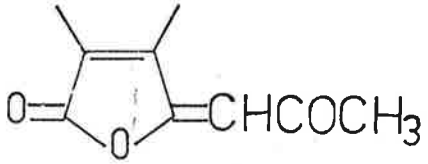
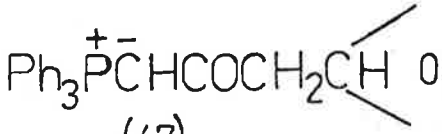
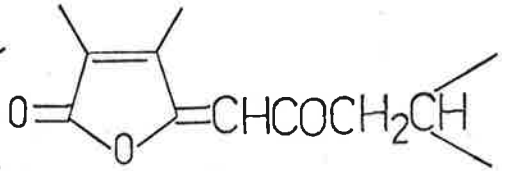
 (43)	(34)	 (44) + (45)	62	37
(43)	(6)	 (46)	-	91
(43)	 (47)	 (48)	19	-

TABLE 1 cont.

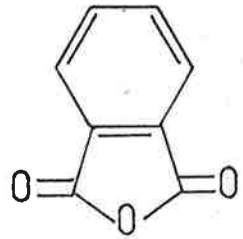
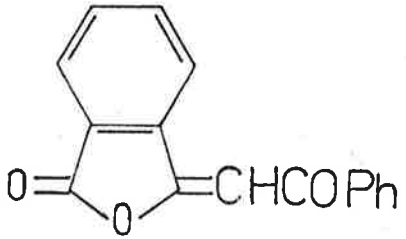
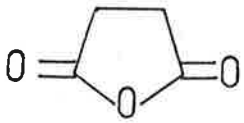
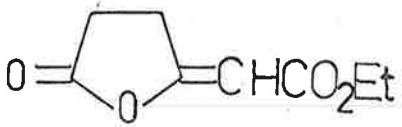
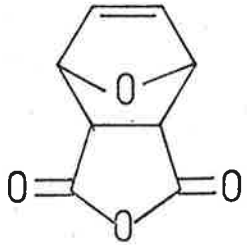
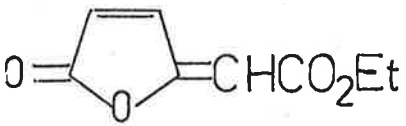
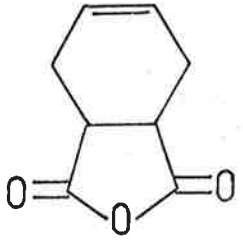
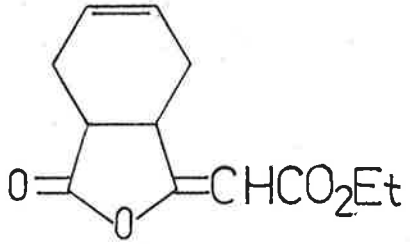
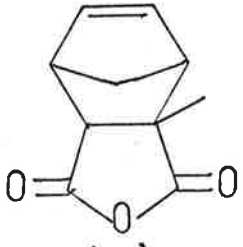
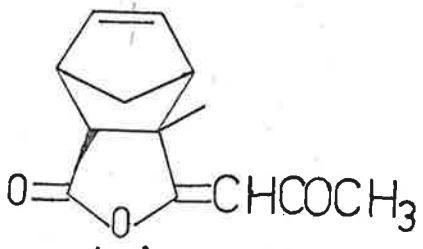
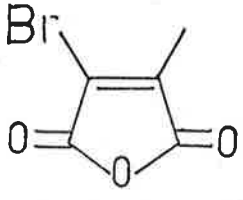
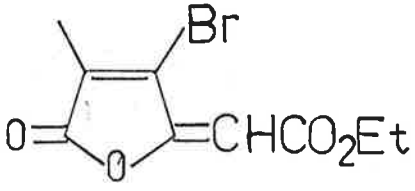
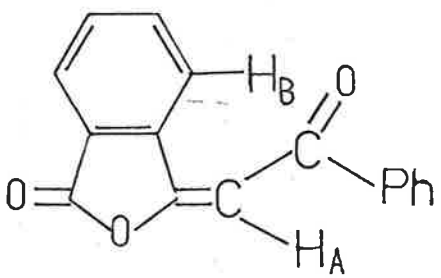
 (49)	$Ph_3\overset{+}{P}\overset{-}{C}HCOPh$ (50)	 (51)	45	–
 (52)	(34)	 (53)	70	–
 (36)	(34)	 (38) + (37)	(50) trace	– –

TABLE 1 cont.

 (54)	(34)	 (55)	94[2]	-
 (29)	(6)	 (56)	60	-
 (28)	(34)	 (57) + (58)	13	25

The results summarised in Table 1 should be contrasted with those observed for glutaric, benzoic and acetic anhydrides,[22] where the acylated phosphorane was obtained.

The reaction is not stereospecific, although in most cases only the cis product could be isolated. However when both isomers were isolated they were readily separable by chromatography on silica gel. The n.m.r. data for the previously uncharacterized enol-lactones (53) and (37) is given in Tables 2 and 3.

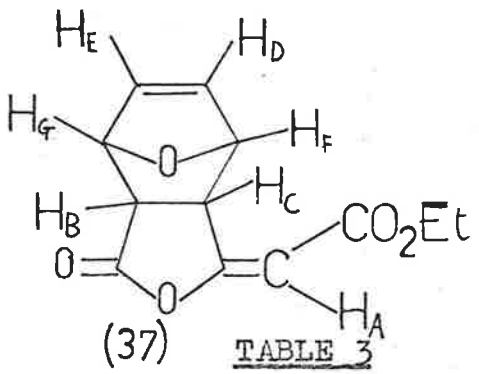


(51)

TABLE 2

τ p.p.m.	Appearance	Proton Count	Assignment
2.9	singlet	1	H_A
1.1	singlet	1	H_B
1.9-2.8	multiplet	8	aromatics

The very low absorption of proton H_B is due to the close proximity of the carbonyl group when the enol-lactone exhibits cis stereochemistry. This contrasts with the stereochemistry reported by Chopard[3] for this compound as trans.



(37)

TABLE 3

τ p.p.m.	Appearance	Proton Count	Assignment
4.65	singlet	1	H_A
8.67	triplet	3	CH_3 of ester
5.78	quartet	2	CH_2 of ester
7.1	doublet	1	H_B
6.2	doublet of doublets	1	H_C
4.3	doublet	1	H_E
4.1	doublet	1	H_D
3.4	multiplet	2	H_F, H_G

On sublimation the adduct (37) underwent a retro Diels-Alder reaction to yield the cis enol-lactone (38). This confirmed the stereochemistry of the Diels-Alder enol-lactone (37) as cis since the absorption (4.65 τ) of proton H_A in the adduct placed it in the general range (4.3-4.7 τ) of trans enol-lactones.

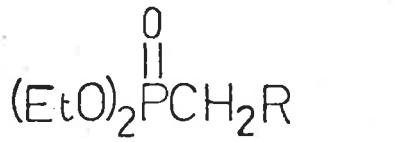
The enol-lactones are thermally stable considerably above the reaction temperatures employed. When the enol-lactones (2), (3), (39), (40), (44), (45), (46) and (53)

were heated in decalin at 100°, thin layer chromatography indicated that formation of the other isomer did not occur. However on distillation of the cis enol-lactone (48), thin layer chromatography indicated the presence of the trans isomer and an n.m.r. spectrum showed that an equal proportion of cis and trans were present. Fowler and Seltzer[36] heated the trans enol-lactone (33) in hot chloroform for four hours and reported that 27% isomerisation to the cis isomer occurred, although they did not isolate the product. Since all this equilibration work was only qualitative and not quantitative the isomerisation data is not conclusive and more investigation is required.

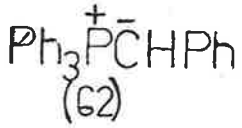
In an attempt to extend the application of the Wittig reaction, anhydrides were treated with phosphonate anions and reactive phosphoranes. Burford[7] and Ingham[8] investigated the Wittig reaction between phthalic anhydride (49) and the Diels-Alder adduct (36) with a variety of stabilised phosphonate anions (59) and (60), unstabilised phosphonate anions (61) and reactive phosphoranes (62) and (63).

(59) $R = C_2H_5$, $R_1 = OC_2H_5$

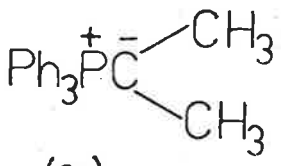
(60) $R = R_1 = CH_3$



(61) R = alkyl or aryl.



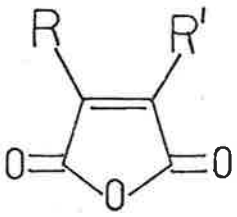
(62)



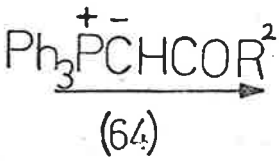
(63)

Enol-lactones were not formed in any of the reactions and starting materials rarely recovered. Thus it appears that enol-lactones can only be prepared from anhydrides and stable phosphoranes.

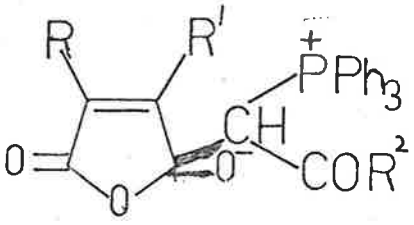
Initial nucleophilic attack by the phosphorane (64) on the anhydride (65) presumably gives the phosphonium betaine (66).



(65)

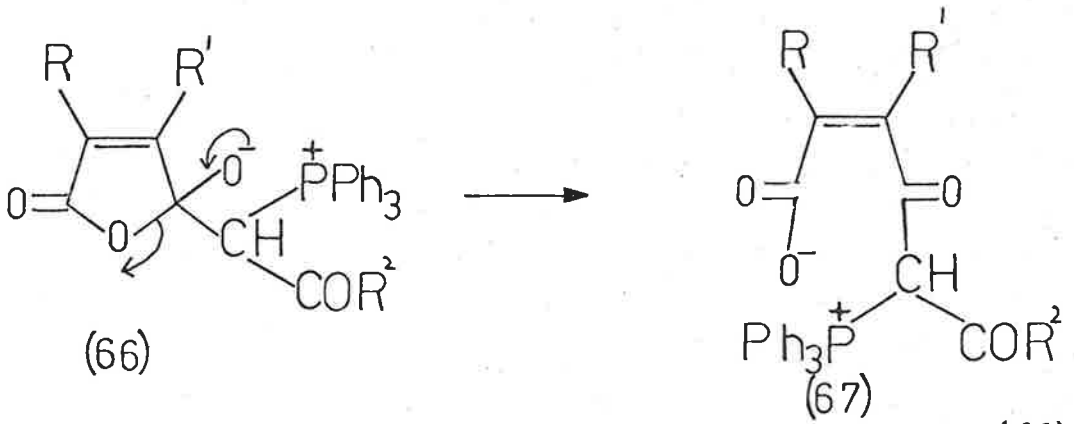


(64)



(66)

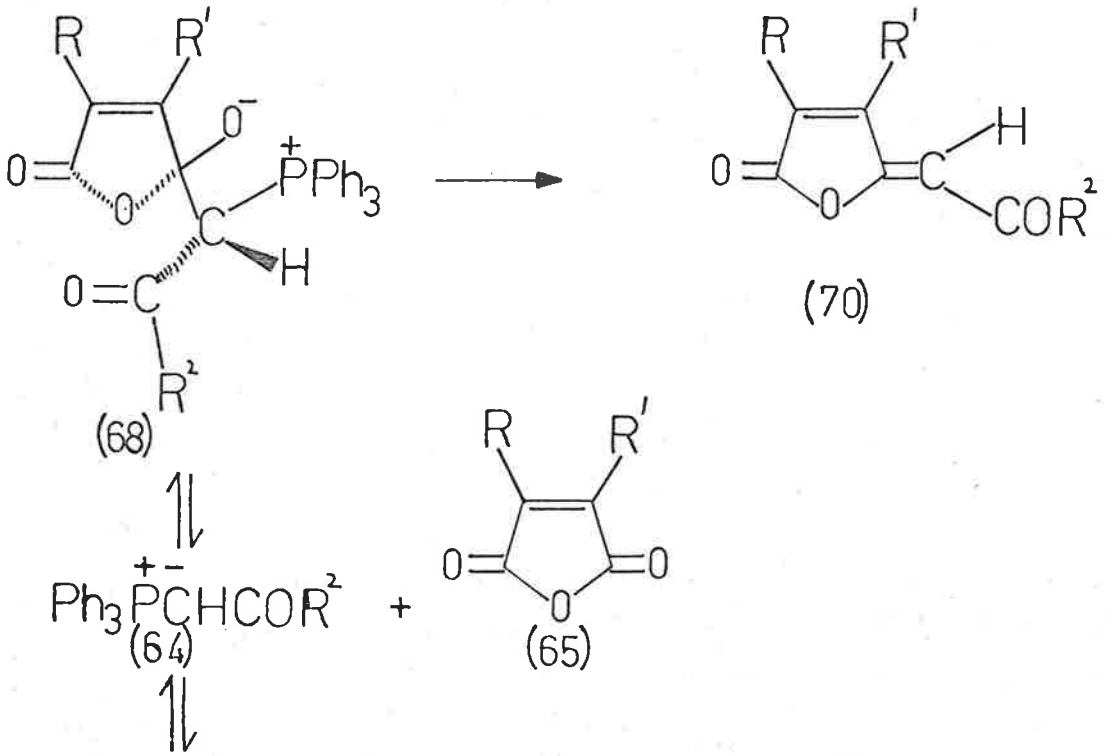
After the formation of a P-O bond the betaine collapses into triphenyl phosphine oxide and enol-lactone. The possibility of the betaine (66) opening to give the new phosphonium salt (67) may explain the presence of unidentified products.



(66) (67)

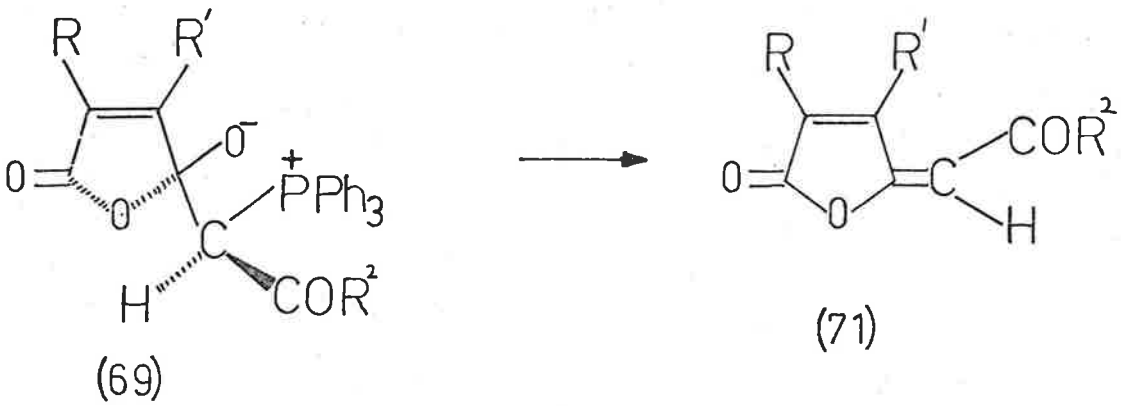
A consideration of the structure of the betaine (66) is necessary in order to predict the stereochemistry of the products.

Since the reaction between stable phosphoranes and carbonyl groups is a slow reversible formation of the betaine[24-26], it is assumed that the resonance stabilised phosphorane (64) is in equilibrium with the two betaines (68) and (69), and as the reaction is reversible it may proceed predominantly by way of the more stable betaine. (Scheme 4).



(68) (70)

(64) (65)



Scheme 4

A study of molecular models indicates that both steric and dipolar repulsion factors must be considered in determining the relative stability of the betaines (68) and (69). Steric factors indicate that the $-COR^2$ group is more easily accommodated in betaine (68) leading to the trans product (70). However as cis products are predominantly isolated it is proposed that the dipolar repulsion between the lactone oxygen and the oxygen of the $-COR^2$ group is the more critical of the two factors. Molecular models reveal the close proximity of these two oxygens in the betaine (68) and therefore betaine (69) is favoured, the product being the cis enol-lactone (71).

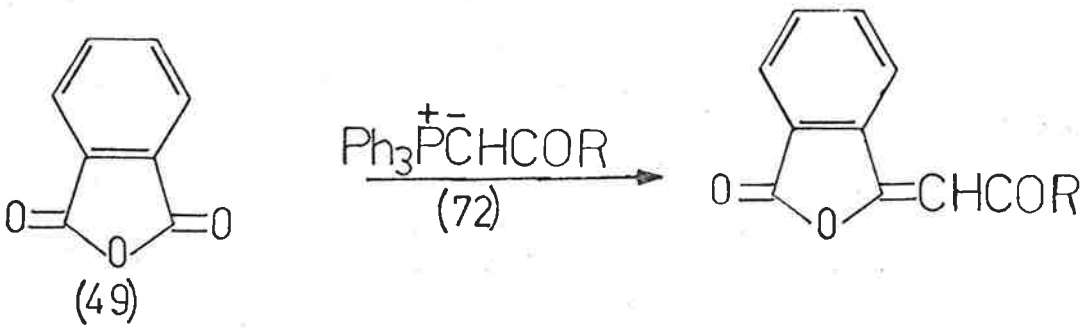
The effect of dipolar repulsion in determining the conformation of a compound has been observed in numerous examples. In biacetyl,[38] the two acetyl groups are not coplanar but instead twisted because of the dipolar repulsion between the oxygen atoms. Dipolar repulsion between bromine

and oxygen explains the axial conformation of the bromine in 2-bromocyclohexanone[39] and the bromination of 2α-methylcholestan-3-one,[40,41] where the product exists in the less stable boat conformation.

The nature of the phosphorane also has an effect on the stereochemistry of the product. Treatment of anhydrides with ethoxycarbonylmethylidene triphenyl phosphorane (64) (R^2 = OEt) yields predominantly the cis enol-lactone. The strong electron donating ethoxy group increases the polarity of the carbonyl group, thus increasing the dipolar repulsion between the carbonyl and lactone oxygens in betaine (68) and thereby favouring the formation of the cis enol-lactone (71) via betaine (69). Treatment of alkylcarbonylmethylidene triphenyl phosphoranes (64) (R^2 = alkyl) with anhydrides yields either mixtures of cis and trans enol-lactones or only the trans enol lactone. In this case the weak electron donating effect of the alkyl group does not markedly increase the dipolar repulsion in betaine (68) and steric factors may become more important. When, for example, R^1 in the anhydride is a methyl group, the steric hindrance between this methyl group and the $-COR^2$ residue in betaine (69) may predominate over dipolar repulsion factors, leading to the formation of trans enol-lactone (70) via betaine (68).

The results obtained by Chopard[3] can now be

explained in terms of dipolar repulsion. In the reaction between phthalic anhydride (49) and various stable phosphoranes (72) he obtained exclusive formation of <u>cis</u> enol-lactones when R was a strong electron-donating group (R = NR_2, OMe, OEt) and <u>trans</u> when R was a weak electron-donating group (R = Me).



(49)

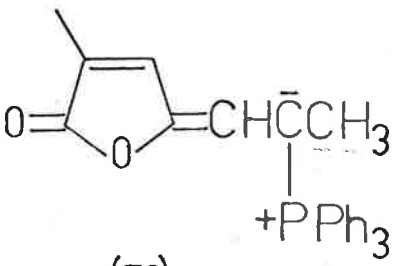
It has not been established whether the <u>cis</u> and <u>trans</u> enol-lactones are formed directly or whether one of the isomers is preferentially formed and thermally isomerises to the other isomer. However this is unlikely on the basis of the attempted equilibrations in decalin. It is unknown at this stage whether the failure of the reactive ylids and phosphonate anions to yield enol-lactones with anhydrides, is due to the reaction conditions used or the unfavourability of the equilibrium leading to betaine formation and more investigation is required.

PART I

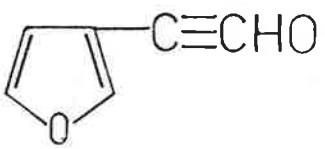
B: THE REACTIONS OF ENOL-LACTONES

INTRODUCTION

Since the proposed synthesis of freelingyne via a Wittig reaction between the enol-lactones (2) and (3) and the phosphorane derived from the acetylenic bromide (4) failed, it was decided to attempt the preparation by using the Wittig reaction in the "opposite sense" i.e., by treatment of the reactive ylid (73) with the acetylenic aldehyde (74).



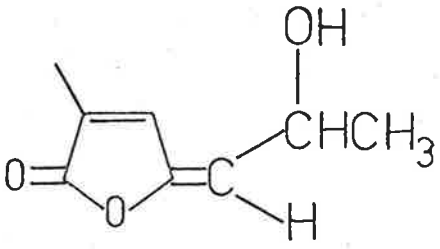
(73)



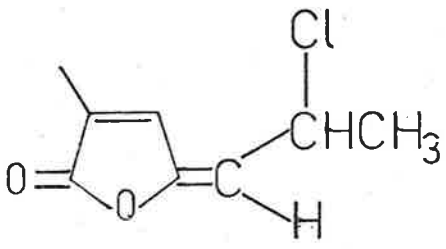
(74)

Treatment of each of the ylids derived from the <u>cis</u> and <u>trans</u> enol-lactones (2) and (3) with the acetylenic aldehyde (74) should yield all four isomers of freelingyne presumably separable in pairs. By using the olefinic aldehyde instead of the acetylenic aldehyde (74) the method should be applicable to the preparation of the dihydro isomers of freelingyne, two of which occur naturally.

Reynolds[2] reported the preparation of the hydroxy lactone (75) from the enol-lactone (2) via sodium borohydride reduction and its conversion to the chloride (76) using thionyl chloride.



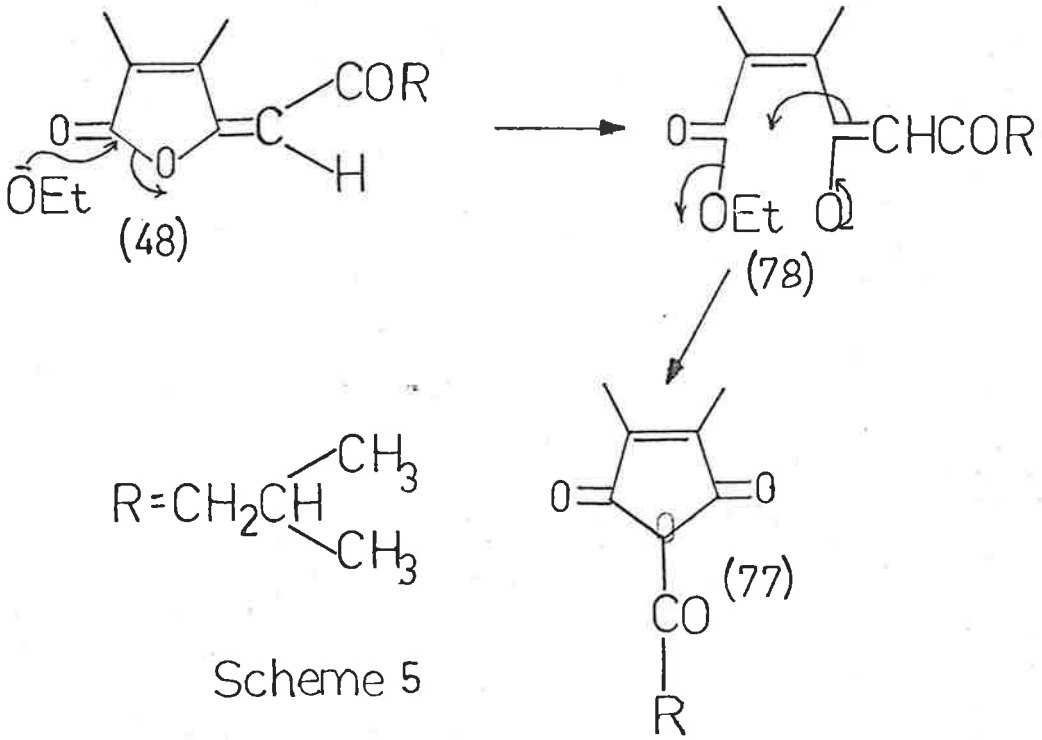
(75)



(76)

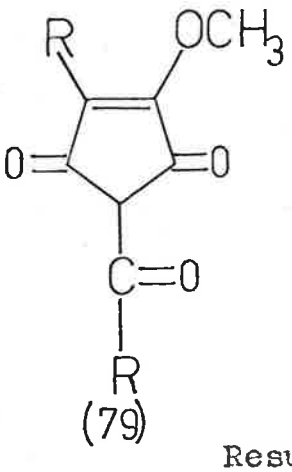
Treatment of the chloride (76) with triphenyl phosphine afforded a colourless salt which immediately decomposed to a dark oil. Since the alcohol (75), chloride (76) and phosphonium salt were never fully characterized it was decided to repeat their preparation using different methods.

The successful preparation[6] of Calythrone (77), involving base catalysed cyclisation of the enol-lactone (48) (scheme 5), indicated considerable synthetic potential for the enol-lactones.

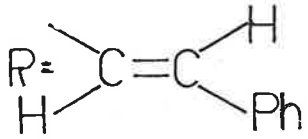


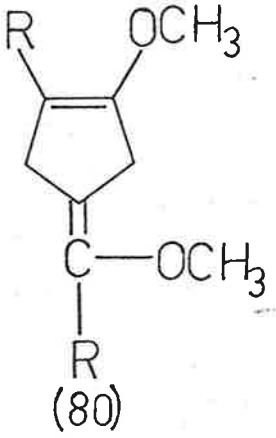
Scheme 5

The extension of the preparation of calythrone to a variety of enol-lactones would provide a convenient synthesis of some natural products containing cyclopentane and cyclopentedione structures. Apart from calythrone[42] which has insecticidal activity, the plant pigments linderone[43] (79) (R = OMe), methyl linderone[43] (80) (R = OMe), lucidone[44] (79) (R = H) and methyl lucidone[44] (80) (R = H) all contain the cyclopentene-1,3-dione nucleus.



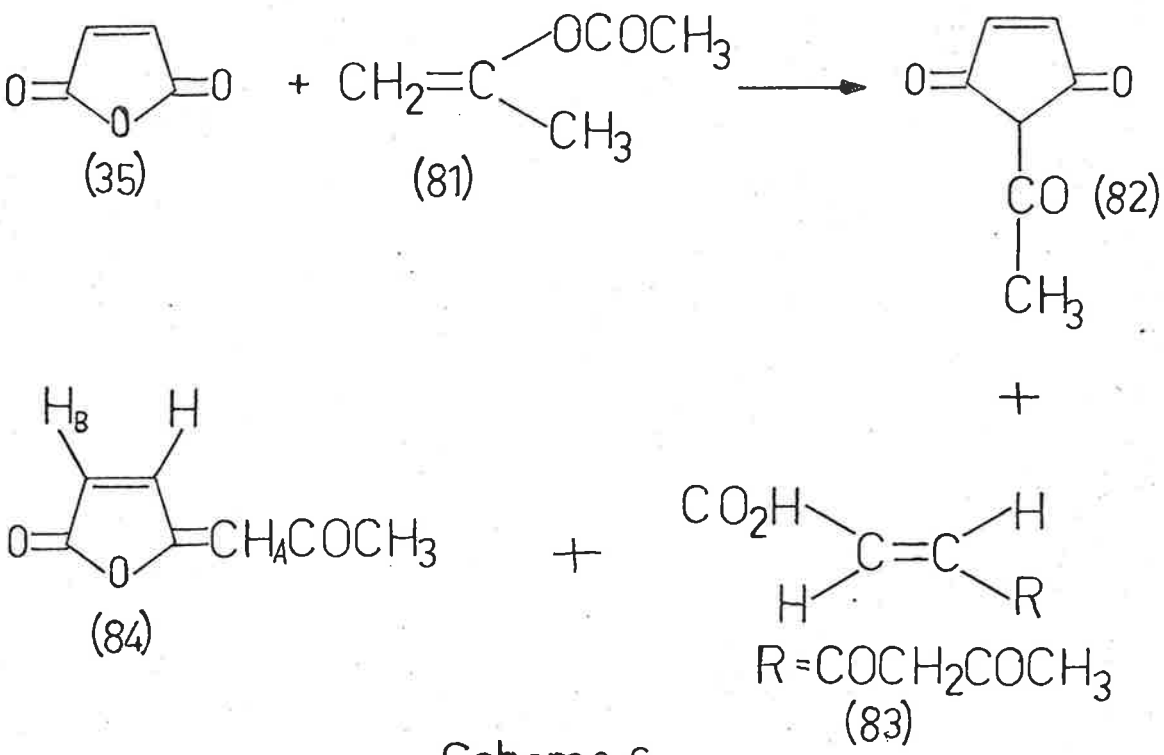
(79)





(80)

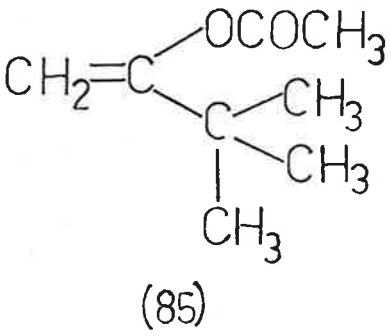
Results[45] of the reaction between isopropenyl acetate and anhydrides of carboxylic acids indicated a general method for the preparation of β-tricarbonyl compounds containing the cyclopentane and cyclopentene-1,3-dione systems. This method was applied to the preparation of acetylcyclopent-4-ene-1,3-diones using maleic anhydride.[46] Isopropenyl acetate (81) reacted readily with maleic anhydride (35) in the presence of aluminium chloride to give 2-acetylcyclopent-4-ene-1,3-dione (82) in 5% yield with fumaryl acetone (83) and the enol-lactone (84) (stereochemistry unspecified) as biproducts. (Scheme 6)



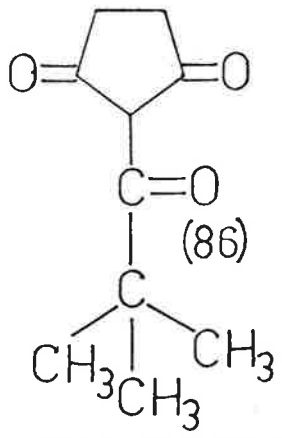
Scheme 6

In a reinvestigation of this reaction, Fowler and Seltzer[36] prepared both isomers of enol-lactone (84) and by a comparison of the coupling constants of H_A and H_B were able to show that the enol-lactone prepared by Merenyi and Nilsson had the cis stereochemistry.

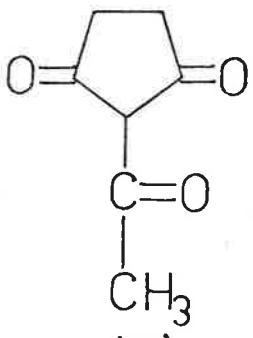
The reaction (i.e., as in scheme 6) was successful using a variety of substituted anhydrides although the yields were very low (c. 5%) in all cases. This reaction is however limited in its application because of the nature of the vinyl ester. Treatment[47] of succinic anhydride (52) with 2-acetoxy-3,3-dimethyl-but-1-ene (85) gave small amounts of 2-pivaloylcyclopentane-1,3-dione (86) and also 2-acetylcyclopentane-1,3-dione (87).



(85)

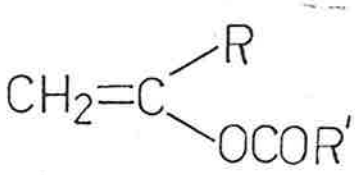


(86)



(87)

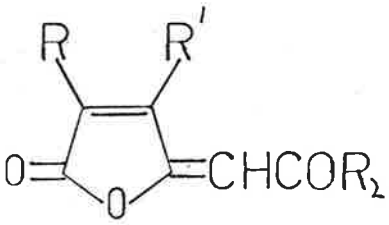
The transacylation thus observed limits the practical scope of the reaction to those 1-substituted vinyl esters where the acyl part and the enol part correspond (R = R' in (88)) as in isopropenylacetate (81).



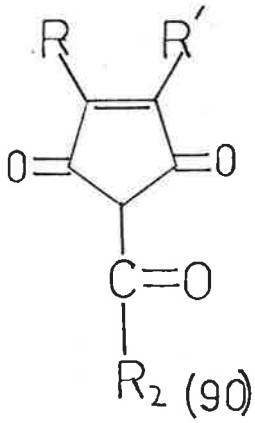
(88)

Spectral studies[48] have shown that the acetylcyclopentene-1,3-diones are completely enolised in solution and in the solid state and this contrasts with the fact that cyclopent-4-ene-1,3-dione is completely ketonic.[49]

Cyclisation of enol-lactones (89) using sodium ethoxide in ethanol should provide a convenient method of synthesis of previously inaccessible β-tricarbonyl compounds (90).

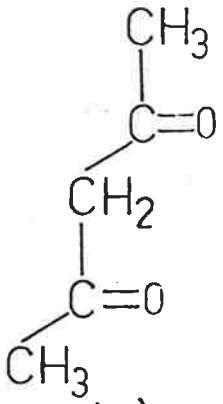


(89)

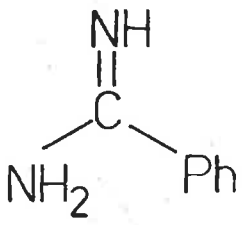


(90)

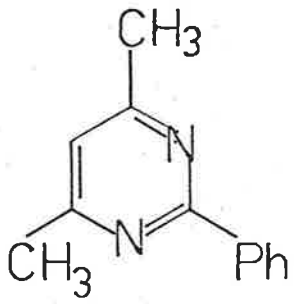
The proposed intermediates in the cyclisation of enol-lactones (e.g. (78)) are enolates of β-diketones which have been used extensively for the preparation of pyrimidines via condensation reactions with a N-C-N fragment. Pyrimidine derivatives occur very widely in nature and several are biologically active. Many synthetic approaches to the pyrimidine nucleus are available.[50,51] The most common synthesis involves the condensation of a three carbon unit to a species having a N-C-N linkage. This general method is extremely versatile because of the large variety of molecules which undergo the condensation. The three carbon unit may be a β-dialdehyde, β-keto-ester, β-diketone etc. The nitrogen-containing unit may be a urea, thiourea, amidine or guanidine. The synthesis is exemplified by the condensation[52] of acetyl acetone (91) with benzamidine (92) to give 4,6-dimethyl-2-phenylpyrimidine (93).



(91)



(92)



(93)

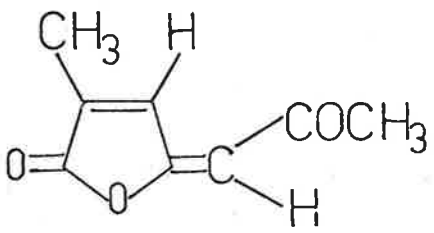
The reaction is usually done under alkaline conditions in ethanol containing sodium ethoxide, but other solvents and even neutral or strongly acidic conditions have often been used to advantage.

Treatment of enol-lactones with urea or thiourea in the presence of sodium ethoxide should lead to another method of preparation of pyrimidines.

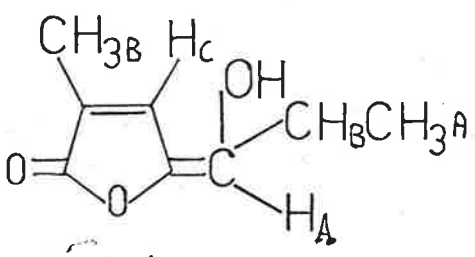
DISCUSSION

The reduction of the enol-lactone (2) using sodium borohydride was repeated under various conditions[6] but the alcohol could not be obtained crystalline. When the reaction was repeated[6] using Reynolds' method, thin layer chromatography indicated a complex mixture of products. This was due to the susceptibility of the lactone to base attack during the borohydride reduction. Preparative plate chromatography resulted in the isolation of a colourless oil. The n.m.r. and infrared spectra indicated the presence of the hydroxy lactone (75) and also slight impurity which presumably prevented the crystallisation of the oil.

Gensler[53] has reported that the use of ethereal zinc borohydride solutions provided a method for reducing carbonyl groups under neutral conditions. When the <u>cis</u> enol-lactone (2) was reduced with zinc borohydride, a colourless crystalline solid was obtained and the n.m.r. data (Table 4) confirmed that it was the <u>cis</u> hydroxy lactone (75).



(2)



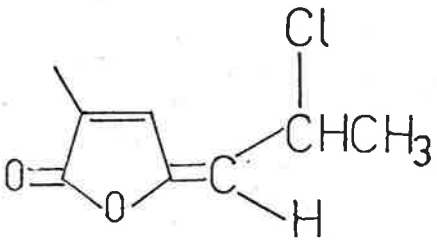
(75)

TABLE 4 -- HYDROXY LACTONE (75)

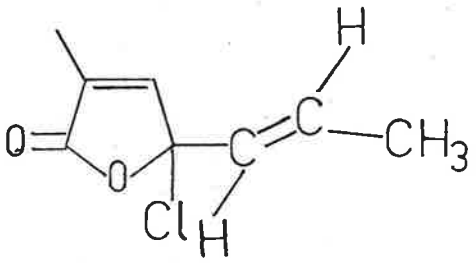
τ p.p.m.	Appearance	Proton Count	Assignment
8.55	doublet	3	CH_3 A
8.10	singlet	3	CH_3 B
6.7	singlet	1	OH
5.7	quartet	1	H_B
4.45	doublet	1	H_A
2.5	multiplet	1	H_C

The signal for the protons of the methyl group A in the hydroxylactone appears as a doublet due to the presence of H_B whereas in the enol-lactone the signal for methyl group A_1 was a singlet. The signal for the hydroxyl group appeared at 6.7τ and disappeared on deuterium exchange. The crystalline hydroxylactone rapidly converted to an oil and accurate analytical figures could not be obtained. The hydroxylactone was therefore prepared when required and used immediately.

The preparation[2] of the chlorobutenolide (76) from the hydroxylactone (75) using thionyl chloride and tri-n-butylamine was repeated[6] but a stable product could not be isolated.



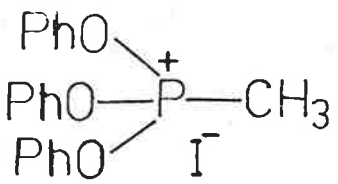
(76)



(94)

This may have been due to the choice of reaction conditions or the result of allylic chlorination resulting in the preparation of the unstable chloride (94). It was decided to investigate other methods of halide preparation.

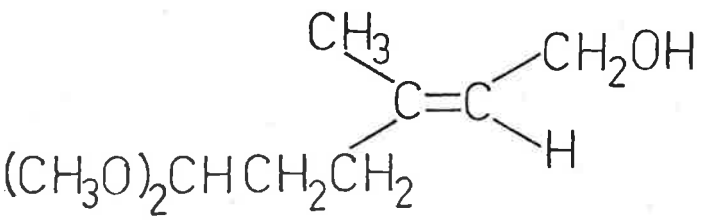
Landauer and Rydon[54] prepared a variety of alkyl iodides from alcohols using triphenylphosphite methiodide (95).



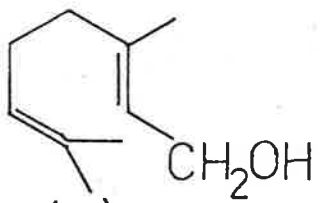
(95)

They were able to prepare several allylic iodides using this method. When the hydroxylactone (75) and triphenyl phosphite methiodide (95) were allowed to stand in tetrahydrofuran solution, unchanged hydroxylactone was recovered. This may have been due to the rapid hydrolysis of the iodide when the tetrahydrofuran solution was added to water. Several modifications of the reaction were attempted but all resulted in failure to isolate the corresponding iodide.

Stork[55] has recently reported the preparation of allylic chlorides from the corresponding alcohols. Treatment of either the alcohol (96) or geraniol (97) in ether and hexamethylphosphoramide with paratoluenesulphonyl-chloride and lithium chloride in ether and hexamethyl-phosphoramide gave high yields of the corresponding unrearranged chlorides.



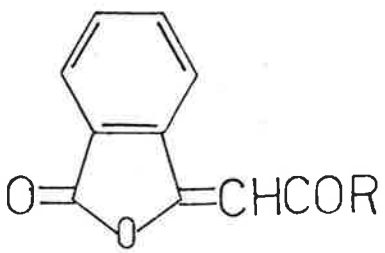
(96)



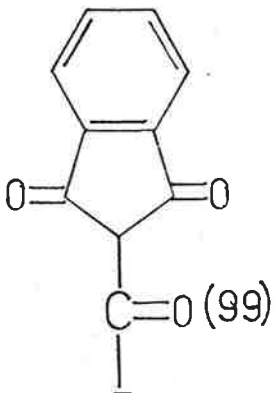
(97)

However treatment of the hydroxylactone under similar conditions did not yield the chloride. All attempts to repeat Stork's experiments failed and at this stage the preparation of the halo-butenolide was discontinued.

Chopard[3] treated enol-lactones (98) with sodium methoxide and isolated the 2-substituted indane-1,3-diones (99).



(98)



(99)

R=NR_2, OCH_3, OEt, Ph, CH_3.

When the enol-lactone (48) was treated with sodium ethoxide, calythrone (77) was isolated in high yield. The previous method of synthesis of Calythrone was reported by Elliot and Jeffs[56] who reacted isobutylmethylketone with dimethyldimethylmaleate in the presence of sodium hydride and obtained a low yield of calythrone as a bi-product. This improved method of cyclopentenedione formation (i.e. base catalysed cyclisation of enol-lactones) was successfully applied to the enol-lactones (2), (3), (44), (45), (46) and (51) as summarised in Table 5.

TABLE 5

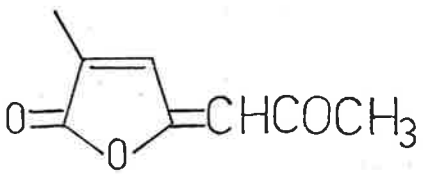
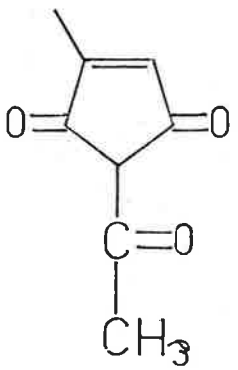
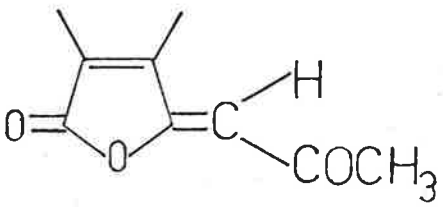
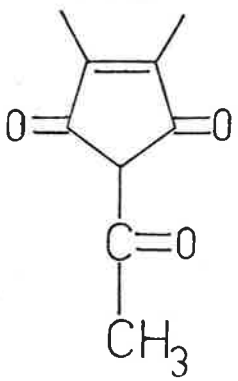
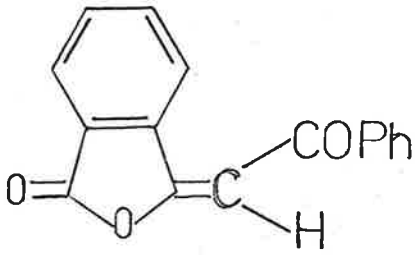
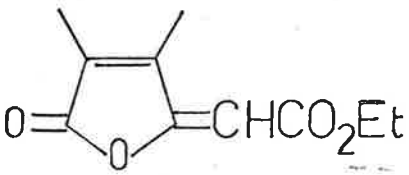
Enol-lactone	Cyclopentene-1,3-dione
 (2) or (3)	 (100)
 (46)	 (101)

TABLE 5 CONTINUED

Enol-lactone

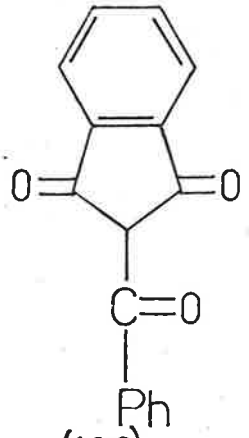


(51)



(44) or (45)

Cyclopentene-1,3-dione



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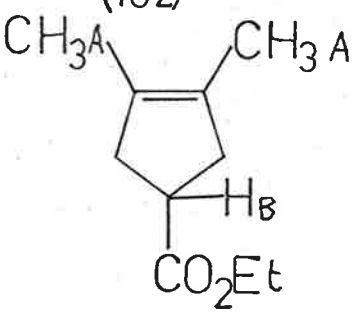
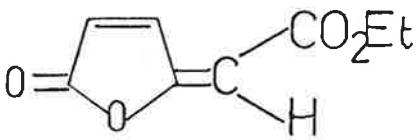


(103)

TABLE 6 -- CYCLOPENTENE-1,3-DIONE (103)

τ p.p.m.	Appearance	Proton Count	Assignment
8.7	triplet	3	CH_3 of ester
7.9	singlet	6	CH_3 A
6.25	singlet	1	H_B
5.75	quartet	2	CH_2 of ester

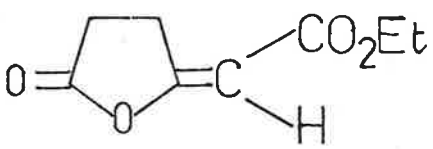
When the enol-lactone (38) was treated with sodium ethoxide a small amount of unidentified product was obtained. The reaction was probably complicated by a Michael-type addition of ethoxide across the activated double bond of the enol-lactone leading to polymer formation. This was analogous to the inability to prepare enol-lactones using



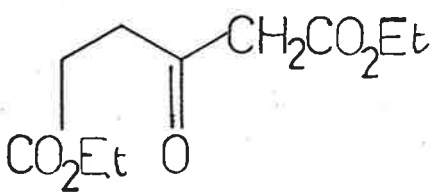
(38)

maleic anhydride because of nucleophilic addition of the phosphorane to the activated double bond.

Treatment of the enol-lactone (53) with sodium ethoxide gave a quantitative yield of diethyl-3-ketoadipate (104).

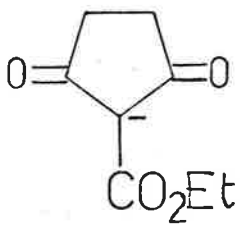


(53)



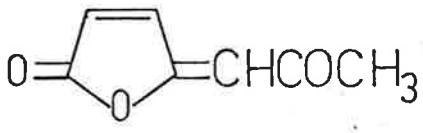
(104)

The formation of the open chain compound (104) is presumably due to the instability of the anion (105) of the acylcyclopentane-1,3-dione.

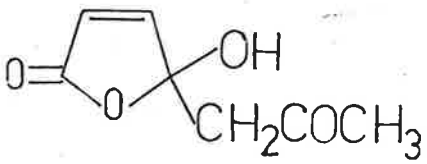


(105)

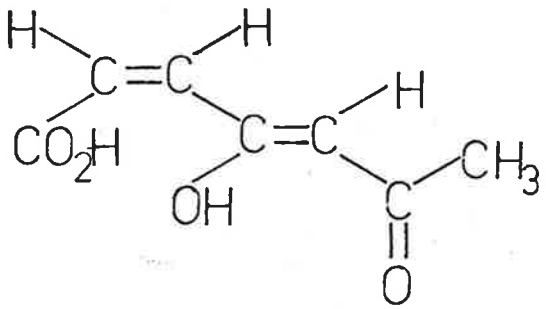
In contrast to the treatment of enol-lactones with ethoxide where cyclisation occurred, Fowler and Seltzer[36] have recently reported that treatment of enol-lactone (32) or (33) with sodium hydroxide gave maleylacetone as a mixture of the closed "pseudo" acid (106) and the open enol acid (107).



(32) or (33)



(106)

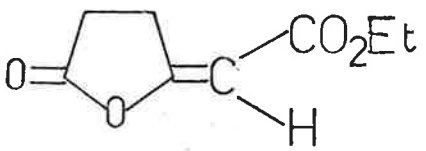


(107)

The preparation of pyrimidines via condensation between β-dicarbonyl compounds and urea, thiourea etc. has been observed many times and this suggested that enol-

lactones should also be applicable.

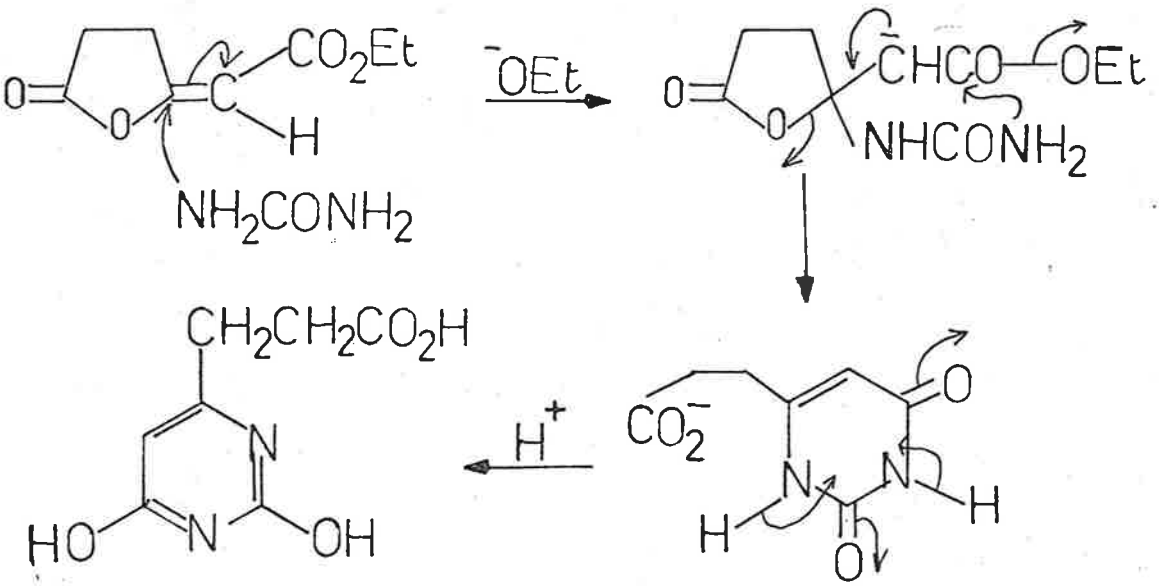
The enol-lactone (53) was treated with urea and sodium ethoxide and gave a high yield of the pyrimidine (108).



(53)

(108)

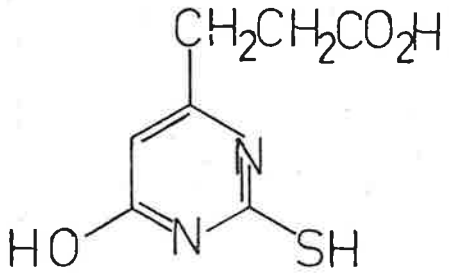
When diethyl-3-ketoadipate (104) was treated under identical conditions, the pyrimidine (108) was again obtained. The proposed mechanism is shown in scheme 7.



Scheme 7

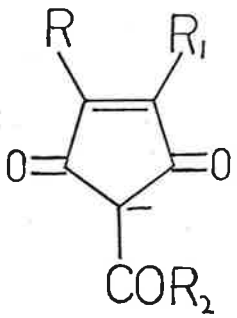
Analysis indicated that the pyrimidine was hydrated with one molecule of water. This is a common observation with many pyrimidines. When the experiment was

repeated using thiourea, the thiolpyrimidine (109) was isolated in high yield.



(109)

Treatment of the enol-lactones, (2), (3), (44), (45), (46) and (51), containing a double bond in the 2-position of the butenolide, with urea or thiourea and sodium ethoxide resulted in the isolation of the acylcyclopentenediones as before. Pyrimidine formation was not observed and this is probably due to the stability of the anion (110) of the acylcyclopentenediones which would be expected to be greater than that in the acylcyclopentanediones (105).



(110)

PART II

SOME SKELETAL REARRANGEMENT PROCESSES OF PHOSPHORANES UPON ELECTRON IMPACT

INTRODUCTION

A recent survey[57] of the mass spectra of alkylidene phosphoranes has led to the discovery of a variety of skeletal rearrangement processes. The formation of triphenylphosphine oxide was noted in many of these spectra but the authors were unable to decide whether this was due to impurity, thermal decomposition or skeletal rearrangement induced by electron impact. In addition peaks due to the fluorenyl cation (m/e, 165) were observed in all spectra. The mass spectrum of the acyl phosphoranes (Table 7) have been studied in order to observe the bond-forming processes occurring upon electron impact[58-60] and the formation of the fluorenyl cation.[60-64]

TABLE 7

$(C_6R^1_5)_3P{=}CR^2{-}COR^3$

	R^1	R^2	R^3
(6)	H	H	Me
(111)	D	H	Me
(112)	H	H	CH_2Cl
(113)	H	H	Et
(114)	H	H	cyclo C_3H_5
(47)	H	H	isobutyl

continued overleaf

TABLE 7 CONTINUED

$(C_6R^1{}_5)_3P{=}CR^2{-}COR^3$

	R^1	R^2	R^3
(41)	H	H	t-butyl
(50)	H	H	Ph
(115)	D	H	Ph
(116)	H	D	Ph

As the normal fragmentation patterns in the spectrum of phenylcarbonylmethylidene triphenyl phosphorane (50) have been reported,[57] only reactions involving P-O bond formation, the formation of m/e 165 and a particular process which aids structure elucidation will be considered.

DISCUSSION

Fig. 1

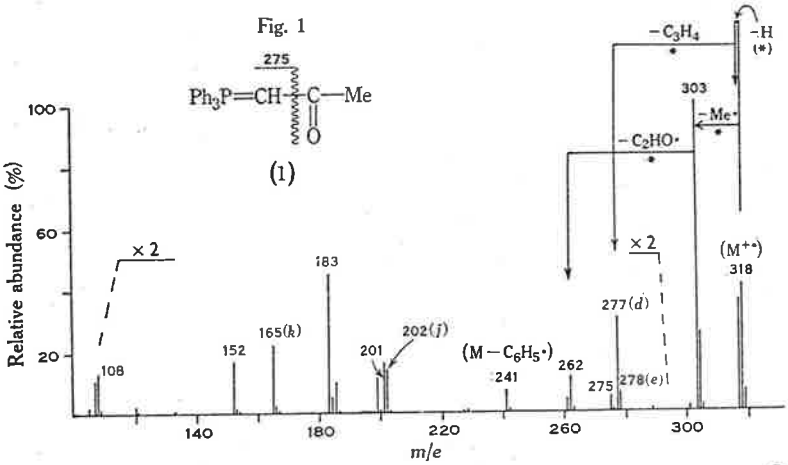


Fig. 2

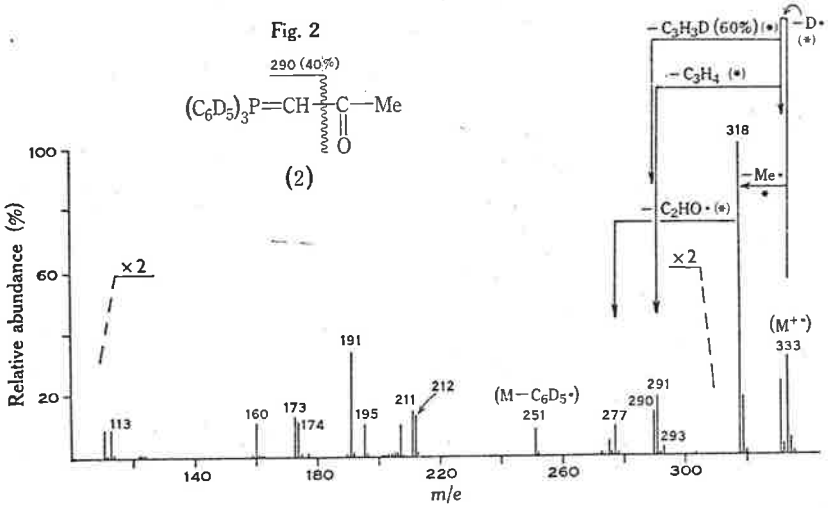


Fig. 3

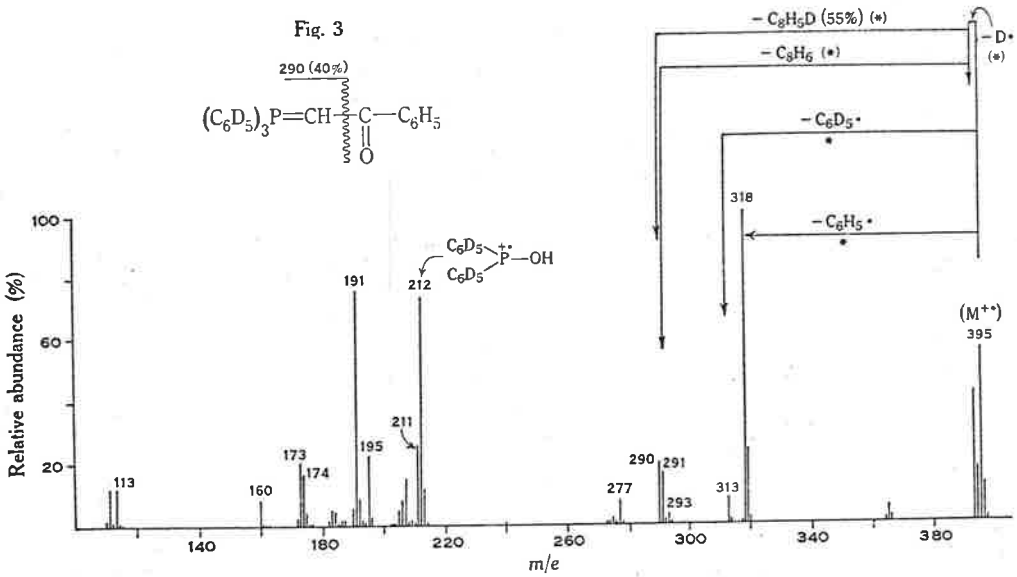
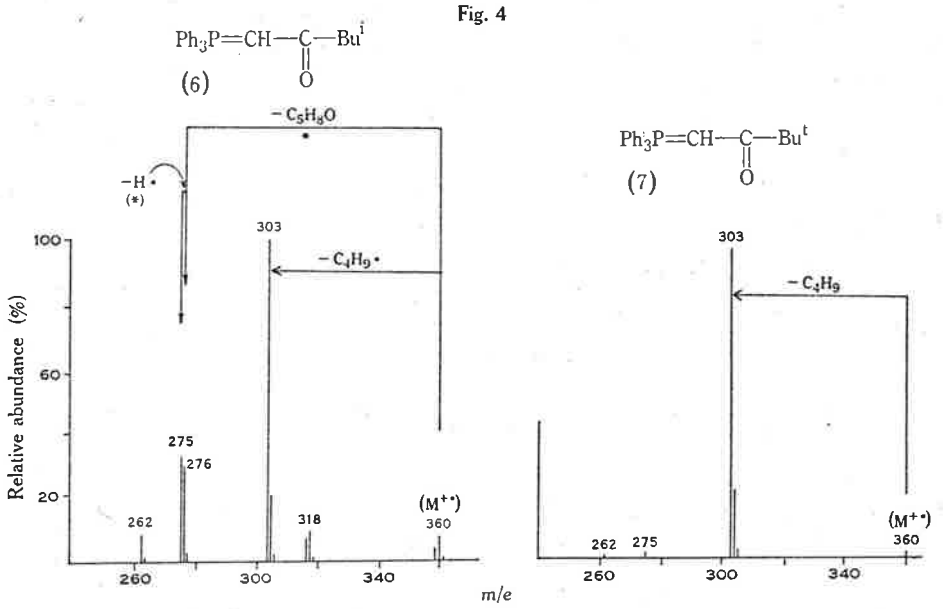


Fig. 4



Representative spectra are recorded in Figures 1-4. The compositions of rearrangement ions have been established by exact mass measurement.

The phosphoranes used for this study were repeatedly crystallised to remove any trace impurity of triphenylphosphine oxide. If the mass spectra of the phosphoranes (see Table 7) are determined by introduction of the sample through the all-glass heated inlet system at 200°, thermal decomposition[65] occurs, and the resultant spectra are dominated by the spectra of triphenyl phosphine and triphenylphosphine oxide. If the spectra are determined at approximately 70° by the "direct insertion" technique, thermal decomposition does not occur.

TABLE 8

ABUNDANCES OF SOME REARRANGEMENT FRAGMENTS IN THE SPECTRA OF PHOSPHORANES

Compound	m/e 278	m/e 277	m/e 202	m/e 165
6	3	15	7	11
112	0.5	4	2	8
113	--	--	--	5
114	2	9	7	15
47	--	--	--	12
41	--	--	--	14
50	6	32	69	41

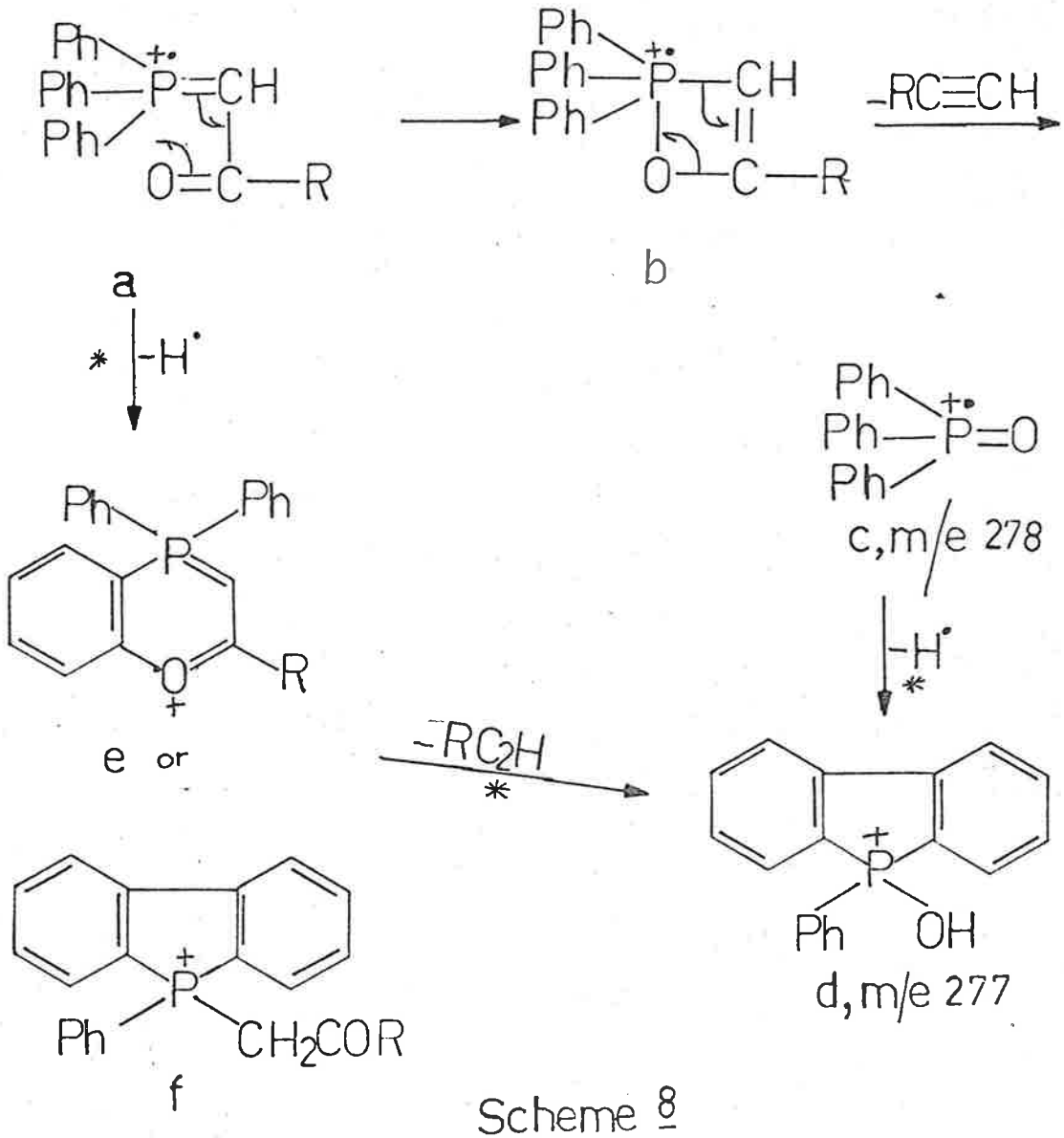
This was verified in the following ways:

(a) The spectra of phosphoranes (113), (47) and (41) contained no peaks due to triphenylphosphine oxide.

(b) Although the spectra of phosphoranes (6), (112), (114) and (50) do contain the rearrangement peaks (see Table 8) an increase in probe temperature from 50-100°C does not affect the abundances of the rearrangement peaks.

(c) As control experiments indicated that triphenylphosphine oxide was much more volatile than the phosphoranes under the above operating conditions, its spectrum could be obtained before the phosphorane volatilized and in this way minute impurities of triphenylphosphine oxide could be detected. None was observed in the purified

phosphoranes.



Scheme 8

The skeletal rearrangement species c and d (scheme 8) are observed in the spectra of phosphoranes where the substituent attached to the carbonyl group is CH_3 (6), CH_2Cl (112), cyclo-C_3H_5 (114), (see Figures 1-3), or Ph (50) (Figure reproduced elsewhere[57]).

Species d (m/e 277) may be formed via two alternate pathways:

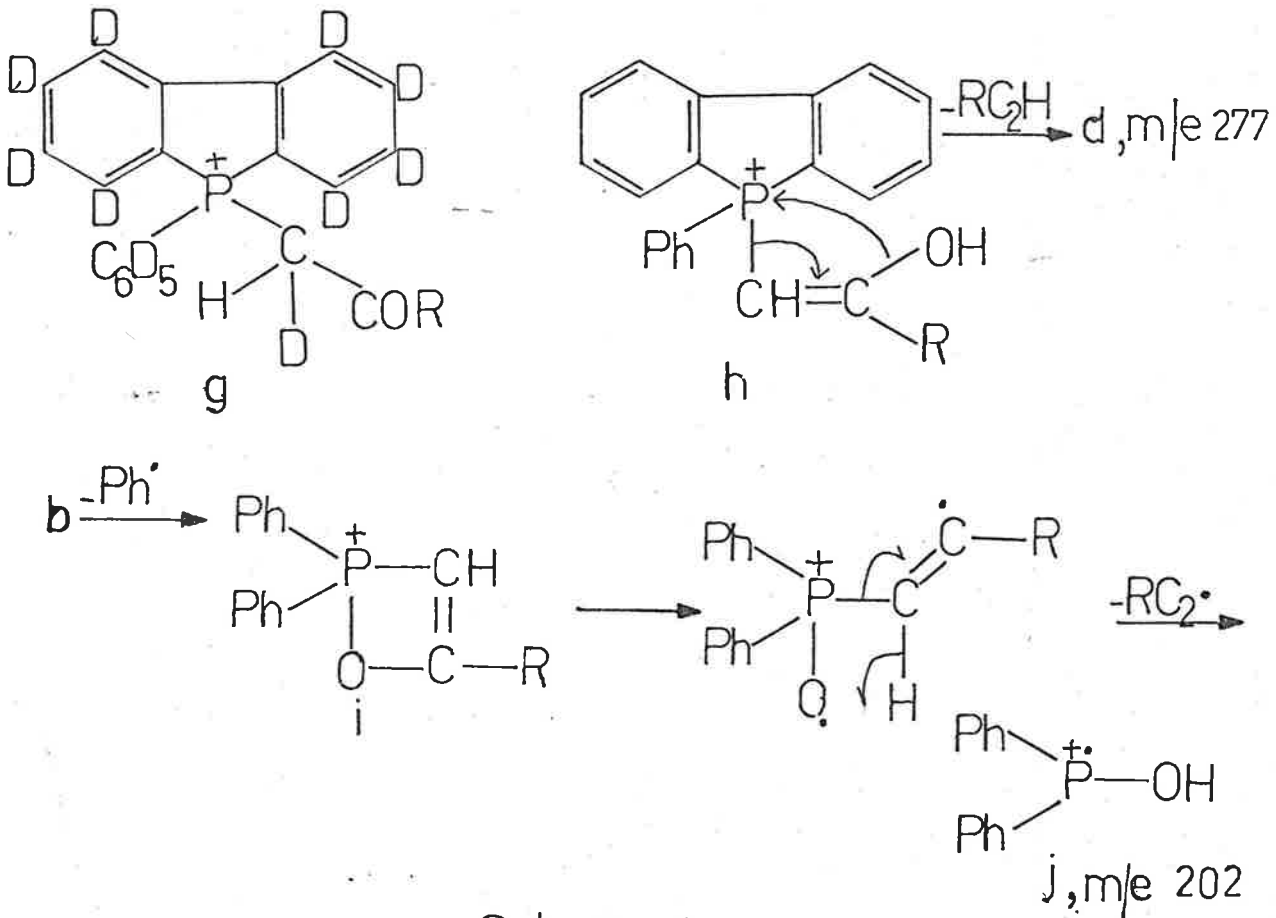
(a) Loss of a hydrogen atom from the triphenylphosphine oxide radical ion (c, m/e 278), which is presumed, in turn, to be formed from the rearranged molecular ion 6, although this process is not substantiated by a metastable peak.

(b) Direct formation of d from the M-1 ion, substantiated in the spectra of phosphoranes (6), (112), (114) and (50) by pronounced metastable ions. The spectra of the deuterated phosphoranes (111) and (115) (Figures 2 and 3) indicate that the hydrogen radical lost during this process came from the phenyl rings attached to phosphorus, and it has been shown for other alkylidene phosphoranes that the hydrogen originates from the ortho (or para) positions of the phenyl ring[57].

Williams and co-authors have proposed two possible structures (e and f) for this ion, and have provided marginal evidence in favour of f. The spectra of the two d_{15} phosphoranes (111) and (115) and the d_1 phosphorane (116) support this proposal. The spectra of phosphoranes (6) and (50) (Figures 1 and 3) show the processes $[M-H^{\bullet}]^{+} \xrightarrow{*}$ m/e 277(d) but in those of d_{15} deuterated phosphoranes (111) and (115) this process becomes $[M-D^{\bullet}]^{+} \xrightarrow{*}$ m/e 291 and $[M-D^{\bullet}]^{+} \xrightarrow{*}$ m/e 290. Similarly that of the d_1 deuterated phosphorane (116) exhibits the two processes $[M-H^{\bullet}]^{+}-C_8H_6 \xrightarrow{*}$ m/e 278 and $[M-H^{\bullet}]^{+}-C_8H_5D \xrightarrow{*}$ m/e 277. It can be calculated (from the spectra of phosphoranes (6), (111),

(50), (115) and (116)) that the two processes in the spectra of the deuterated derivatives occur in the approximate ratio of 1 : 1. Such a decomposition cannot be rationalized on the basis of structure e.

However if f represents the M-1 species, the corresponding ion in the spectra of the d_{15} deuterated phosphoranes (111) and (115) will be g (scheme 9). Fragmentation of this ion through an enol form (e.g. h ⟶ d) may produce m/e 290 and m/e 291 (1 : 1) in their spectra.



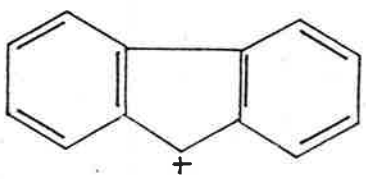
Scheme 9

Another ion (j, m/e 202 ($C_{12}H_{11}PO$)) which is observed in the spectra of phosphoranes (6), (112), (114)

and (50) owes its genesis to P-O bond formation. This species which is not present in the mass spectrum[66] of triphenylphosphineoxide is most pronounced in the spectrum of phosphorane (50) (Figure 3) where it constitutes 69% of the base peak. Metastable peaks, which would substantiate its mode of formation, do not appear but the ion shifts specifically to m/e 212 in the spectrum of the d_{15} deuterated phosphorane (115) and mainly to m/e 203 (c.70%) in that of the d_1 deuterated phosphorane (116).

As the molecular ions of phosphoranes (6), (112), (114) and (50) eliminate (to a small extent) a phenyl radical by C-P cleavage (see figures 1-3), a possible mechanism for the major process forming m/e 202 may be b —— j.

f → → →

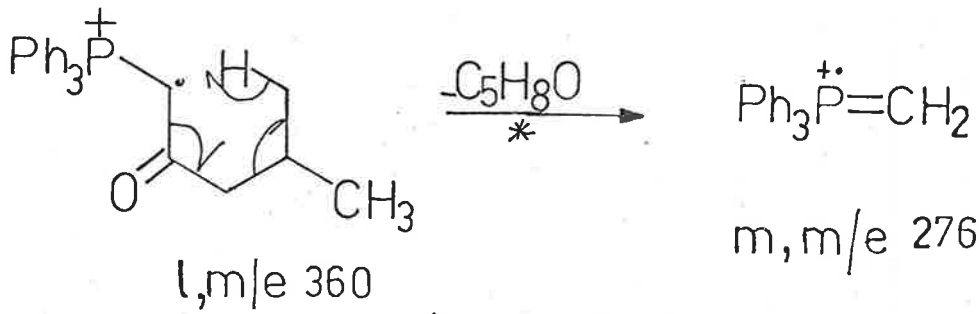


k, m/e 165

Ions corresponding to the fluorenyl cation (k) are observed in the spectra of all the phosphoranes studied and in the initial survey,[57] but are absent in the spectra of triphenyl phosphine,[66] triphenylphosphine oxide[66] and methylenetriphenylphosphorane.[66] In the spectra of phosphoranes (6), (112), (113), (114), (47), (41) and (50) metastable peaks, which would indicate how k is formed, do not appear but deuterium labelling shows which of the

hydrogens are involved. The peak at m/e 165 is shifted to m/e 165 and m/e 166 (1 : 1) in the spectrum of the d_1-deuterated phosphorane (116) and to m/e 173 and m/e 174 (1 : 1) in those of the d_{15} deuterated phosphoranes (111) and (115).

This proves that the fluorene radical ion is not implicated in the rearrangement, as this species is known to undergo hydrogen scrambling prior to elimination of a hydrogen atom.[67] In order to explain the 1 : 1 ratio obtained in the spectra of the labelled derivatives, it is suggested that the precursor may be g (cf. f —— k) with equal loss of H$^\bullet$ or D$^\bullet$ from the methylene group preceding the insertion of the carbon bearing the positive charge into the aromatic system. This ion may then eliminate the acyl (-COR) and C_6D_5P residues to form k. A mechanism involving loss of H$^\bullet$ from the methylene group after cyclisation cannot be discounted, but such a process may be accompanied by hydrogen scrambling.



l, m/e 360

m, m/e 276

The spectra (Figure 4) of the two isomeric butyl phosphoranes (47) and (41) are different in one important

respect. The isobutylcarbonylmethylidene triphenyl phosphorane (47) undergoes the hydrogen rearrangement reaction l —— m from the molecular ion. The ion m fragments analogously to the methylene triphenylphosphorane molecular ion.[66] The presence of this process allows ready differentiation of the isomers.

EXPERIMENTAL

General

Melting points were determined on a Kofler hot stage microscope and are uncorrected. Infrared spectra were recorded on a Unicam SP 200 instrument as Nujol mulls unless otherwise stated. Nuclear magnetic resonance spectra were recorded on a Varian DP-60 and Varian T-60 spectrometer operating at sixty megacycles, in deuterochloroform solutions using tetramethylsilane as internal standard. Mass spectra were recorded on a Hitachi Perkin-Elmer RMU 6D instrument. Microanalyses were performed by the Australian Microanalytical Laboratories, Melbourne. Sorbsil silica gel was used for column chromatography and an equal mixture of Kieselgel G and Kieselgel HF_{254} was used for thin layer chromatography (t.l.c.). Light petroleum refers to the fraction of b.p. 50-60°.

Reaction between citraconic anhydride (5) and methylcarbonylmethylidene triphenylphosphorane (6)

The anhydride and the phosphorane were treated according to Reynolds[2] and chromatography on silica gel gave cis-4-methylcarbonylmethylidene-2-methylbut-2-ene-4-olide (2) (24%) which was recrystallised from light petroleum to give pale yellow needles m.p. 87-89° (lit.[2] 88-89°). A mixture of the trans isomers (22%) was recrystallised from light petroleum to give pale yellow plates m.p. 77-82° (lit.[2] 75-83°). The n.m.r. spectrum showed that the two

trans isomers were obtained in equal proportions.

Reaction between citraconic anhydride (5) and ethoxycarbonylmethylidene triphenylphosphorane (34)

The phosphorane and the anhydride were treated according to Reynolds[2] and chromatography on silica gel gave cis-4-ethoxycarbonylmethylidene-2-methylbut-2-ene-4-olide (39) (60%) which was recrystallised from light petroleum to give colourless crystals m.p. 48-49° (lit.[2] m.p. 47-48°). A trace of the trans isomer (40) (1%) was recrystallised from light petroleum to give colourless crystals m.p. 80-83° (lit.[2] m.p. 75-85°).

Reaction between dimethylmaleic anhydride (43) and methylcarbonylmethylidene triphenylphosphorane (6)

The phosphorane and the anhydride were treated according to Reynolds[2] and chromatography on silica gel gave trans-4-methylcarbonylmethylidene-2,3-dimethylbut-2-ene-4-olide (46) (91%) which was recrystallised from light petroleum to give pale yellow crystals m.p. 108-109° (lit.[2] m.p. 109°).

Reaction between dimethylmaleic anhydride (43) and ethoxycarbonylmethylidene triphenylphosphorane (34)

A solution of dimethylmaleic anhydride (3.15 g, 0.025 mol) in chloroform (20 ml) was added dropwise, under nitrogen, to a stirred solution of the phosphorane (8.7 g,

0.025 mol) in chloroform (20 ml) and the reaction mixture refluxed for twelve hours. The chloroform was removed under reduced pressure and the residue chromatographed on silica gel. Elution with ether/light petroleum gave cis-4-ethoxycarbonylmethylidene-2,3-dimethylbut-2-ene-4-olide (44) (2.8 g, 62%) which was recrystallised from light petroleum to give a colourless crystalline solid m.p. 39-40° (Found: C, 60.7; H, 6.5. Calc. for $C_{10}H_{12}O_4$: C, 61.2; H, 6.1%.) λ max 3050 (=C-H), 1770 (lactone C=O), 1700 (C=O), 1650 cm^{-1} (C=C). The trans enol-lactone (45) (1.75 g, 37%) was distilled as a colourless oil b.p. 100-110°/0.1 m.m. (Found: C, 60.7; H, 6.5. Calc. for $C_{10}H_{12}O_4$: C, 61.2; H, 6.1%) λ max (film) 3030 (=C-H), 1780 (lactone C=O), 1715 (C=O), 1640 cm^{-1} (C=C).

Reaction between dimethylmaleic anhydride (43) and isobutylcarbonylmethylidene triphenylphosphorane (47)

The anhydride and the phosphorane were treated as previously described[6] and chromatography on silica gel gave cis-4-isobutylcarbonylmethylidene-2,3-dimethylbut-2-ene-4-olide (48) (19%) which was distilled to give a colourless oil b.p. 155-160°/0.05 mm. (lit.[6] b.p. 150-160°/0.05 mm.)

Reaction between succinic anhydride (52) and ethoxycarbonylmethylidene triphenylphosphorane (34)

The anhydride and the phosphorane were treated in dimethoxyethane according to Reynolds[2] for 24 hours instead

of 15 hours. Chromatography on silica gel gave cis-4-ethoxycarbonylmethylidenebutyrolactone (53) (70%) which was recrystallised from light petroleum to give colourless needles m.p. 94-96° (lit.[2] m.p. 93-96°).

Reaction between 3,6-endoxo-1,2,3,6-tetrahydrophthalic anhydride (36) and ethoxycarbonylmethylidene triphenylphosphorane (34)

The anhydride (4.15 g, 0.025 mol) in chloroform (60 ml) was added dropwise, under nitrogen, to a stirred solution of the phosphorane (8.75 g, 0.025 mol) in chloroform (30 ml) and the temperature maintained at 48-50° for fifty hours. Removal of the chloroform under reduced pressure and chromatography on silica gel gave cis-4-ethoxycarbonylmethylidenebut-2-ene-4-olide (38) (2.1 g, 50%) which was recrystallised from light petroleum to give colourless crystals m.p. 76-77° (lit.[2] m.p. 75-77°). Further elution gave the cis Diels-Alder adduct enol-lactone (37) (0.3 g, 0.5%) which was recrystallised from ether/light petroleum to give colourless crystals m.p. 97-100° (Found: C, 61.08; H, 5.00. Calc. for $C_{12}H_{12}O_5$: C, 61.01; H, 5.12%.) λ max 3030 (=C-H), 1780 (lactone C=O), 1700 (C=O) 1610 cm^{-1} (C=C). The Diels-Alder adduct sublimed at 80-95°/0.5 mm to give a quantitative yield of the cis butenolide (38).

Reaction between phthalic anhydride (49) and phenylcarbonylmethylidene triphenylphosphorane (50)

The anhydride (5.3 g, 0.036 mol) in chloroform

(40 ml) was added dropwise, under nitrogen, to a stirred solution of the phosphorane (13.7 g, 0.036 mol) in chloroform (40 ml) and the reaction mixture refluxed for 20 hours. Removal of the chloroform under reduced pressure and chromatography on silica gel gave the cis butenolide (51) (4.0 g, 45%) which was recrystallised from light petroleum to give colourless crystals m.p. 118-119°. (Found: C, 76.5; H, 4.05. Calc. for $C_8H_4O_3$: C, 76.8; H, 4.03%.) λ max 1790 (lactone C=O), 1660, 1620 cm^{-1} (C=C).

Reaction between 1,4-endomethylene-3-methylcyclohex-5-enedicarboxylic-2,3-acidanhydride (29) and methylcarbonylmethylidene triphenylphosphorane (6)

The anhydride and the phosphorane were treated as previously described[6] and chromatography on silica gel gave the cis butenolide (56) (60%) which was recrystallised from light petroleum to give colourless crystals m.p. 90-92° (lit.[6] m.p. 90-92°).

Reaction between bromocitraconic anhydride (28) and ethoxycarbonylmethylidene triphenylphosphorane (34)

The reaction conditions were modified from those previously described.[6] The anhydride (3.82 g, 0.02 mol) in chloroform (30 ml) was added dropwise, under nitrogen, to a stirred solution of the phosphorane (7.96 g, 0.02 mol) in chloroform (30 ml) maintained at 0°C. The reaction mixture was stirred at 40-50° C for 24 hours and then at room

temperature for 60 hours. Removal of the chloroform under reduced pressure and chromatography on silica gel gave cis-4-ethoxycarbonylmethylidene-3-bromo-2-methylbut-2-ene-4-olide (57) (0.7 g, 13.4%) which was recrystallised from light petroleum to give colourless crystals m.p. 43-46°. (Found: C, 41.3; H, 3.6; Br, 30.9. Calc. for $C_9H_9BrO_4$: C, 41.4; H, 3.5; Br, 30.6%.) λ max 3100 (=C-H), 1780 (lactone C=O), 1690 (C=O), 1610 cm^{-1} (C=C). The trans isomer (58) (1.3 g, 25%) was recrystallised from light petroleum to give colourless crystals m.p. 48-50°. (Found: C, 40.7; H, 3.6; Br, 29.1. Calc. for $C_9H_9BrO_4$: C, 41.4; H, 3.5; Br, 30.6%.). A trace of trans-4-ethoxycarbonylmethylidene-2-bromo-3-methylbut-2-ene-4-olide (0.05 g, 0.5%) was distilled to give a colourless oil b.p. 150-160°/1 mm. The n.m.r. data has been previously given.[6]

Zinc borohydride

Zinc borohydride was prepared from anhydrous zinc chloride and sodium borohydride according to Gensler et al.[53] The ethereal zinc borohydride was stored in a sealed flask at 0°C.

Reduction of cis-4-methylcarbonylmethylidene-2-methylbut-2-ene-4-olide (2)

A solution of zinc borohydride (0.325 g, 0.0035 mol) in ether (25 ml) was added by means of a syringe to a stirred solution of the enol-lactone (2) (0.152 g, 0.001 mol)

in ether (10 ml) and the reaction mixture stirred at room temperature for five minutes when t.l.c. indicated the absence of enol-lactone. Water (2 ml) was added carefully and the reaction mixture stirred for ten minutes. The ether was decanted from a white solid which was washed with more ether (20 ml). The combined ether extracts were filtered through a short column of silica gel to remove inorganic material and then dried over anhydrous magnesium sulphate. Removal of the ether gave cis-4-(2-hydroxypropylidene)-2-methylbut-2-ene-4-olide (75) (0.3 g, 58%) which was recrystallised from light petroleum (b.p. 60-80°) to give colourless crystals m.p. 54-57°. max 3400 (O-H), 3100 (=C-H), 1750 (lactone C=O), 1660 and 1620 cm^{-1} (C=C). Accurate analytical figures could not be obtained because of the instability of the compound.

Triphenylphosphite methiodide (95)

The methiodide was prepared from triphenylphosphite and methyl iodide according to the method of Landauer and Rydon.[54] It was stored as a yellow crystalline solid under anhydrous ether in a stoppered flask maintained at 0°C.

Reaction between the cis-hydroxylactone (75) and triphenylphosphite methiodide (95)

Triphenylphosphite methiodide (0.15 g, 0.0003 mol) in dry tetrahydrofuran (5 ml) was added dropwise, under nitrogen, to a stirred solution of the cis-hydroxylactone

(0.05 g, 0.0003 mol) in dry tetrahydrofuran (5 ml) maintained at 0°C. After maintaining the temperature at 20° for twelve hours and then refluxing for twelve hours the reaction mixture was carefully added to cold water (5 ml). The solution was extracted with ether (20 ml) but t.l.c. indicated only the presence of unreacted hydroxylactone.

Attempted preparation of the chlorobutenolide (76)

The hydroxylactone (75) (0.15 g, 0.001 mol) in ether (2 ml) and hexamethylphosphoramide (1.0 ml) was treated at room temperature with one equivalent of methyl lithium.[68] Paratoluenesulphonylchloride (0.2 g, 0.001 mole) and lithium chloride (0.12 g, 0.001 mol) in ether (2 ml) and hexamethylphosphoramide (1.0 ml) was slowly added dropwise and the dark reaction mixture was stirred for twelve hours at room temperature. Water (10 ml) was added and the solution extracted with light petroleum. After drying over anhydrous magnesium sulphate and removal of the light petroleum, a dark liquid was obtained and the infra red spectrum suggested the presence of polymeric material.

Attempted preparation of geranyl chloride as described by Stork[55]

Geraniol (97) (3.08 g, 0.02 mol) in ether (10 ml) and hexamethylphosphoramide (5 ml) was treated at room temperature with one equivalent of methyl lithium.[68] Paratoluenesulphonylchloride (4.0 g, 0.021 mol) and lithium

chloride (2.4 g, 0.057 mol) in ether (10 ml) and hexamethylphosphoramide (5 ml) was added dropwise and the dark reaction mixture was stirred for twelve hours at room temperature. Water (20 ml) was added and the solution extracted with light petroleum and dried over anhydrous magnesium sulphate. Removal of the light petroleum gave a dark liquid and the infra red spectrum suggested the presence of polymeric material.

2-benzoylindan-1,3-dione (102)

The enol-lactone (51) (1.0 g, 0.004 mol) was added to sodium (0.184 g, 0.008 g atom) in absolute ethanol (10 ml). After the reaction mixture was refluxed for twelve hours, the ethanol was removed under reduced pressure and the residue dissolved in water. Acidification with oxalic acid solution gave a colourless precipitate and filtration gave the indandione (102) (0.95 g, 95%) which was recrystallised from light petroleum to give a colourless crystalline solid m.p. 109-110° (lit.[69] m.p. 108°)

2-acetyl-4,5-dimethylcyclopent-4-ene-1,3-dione (101)

The trans enol-lactone (46) (0.33 g, 0.002 mol) was added to sodium (0.07 g, 0.003 g atom) in absolute ethanol (10 ml) and the reaction mixture refluxed for twelve hours. The ethanol was removed under reduced pressure, the residue dissolved in water and acidified with oxalic acid solution. Filtration gave the cyclopentene-1,3-dione

(101) (0.32 g, 97%) which was recrystallized from light petroleum to give colourless crystals m.p. 50-51 (lit.[46] m.p. 51-52°).

2-acetyl-4-methylcyclopent-4-ene-1,3-dione (100)

The cis or trans enol-lactone (2) or (3) (0.3 g, 0.002 mol) was added to sodium (0.07 g, 0.003 mol) in absolute ethanol (10 ml) and the reaction mixture refluxed for seven hours. The ethanol was removed under reduced pressure and the residue dissolved in water and acidified with oxalic acid solution. Filtration gave the cyclopentene-1,3-dione (100) (0.29 g, 95%) and recrystallisation from light petroleum gave a colourless crystalline solid m.p. 44-50° (lit.[46] m.p. 45-50°).

2-ethoxycarbonyl-4,5-dimethylcyclopent-4-ene-1,3-dione (103)

The cis or trans enol-lactone (44) or (45) (0.39 g, 0.002 mol) was added to sodium (0.07 g, 0.003 g atom) in absolute ethanol (10 ml) and the reaction mixture refluxed for seven hours. The ethanol was removed under reduced pressure and the residue dissolved in water and acidified with oxalic acid solution. Filtration gave the cyclopentene-1,3-dione (103) (0.35 g, 90%) and recrystallisation from light petroleum gave colourless crystals m.p. 57-58°. λ max 2500-3500 (hydrogen bonded - OH) 1750, 1720, 1690 (C=O'S), 1630 cm^{-1} (C=C).

Attempted cyclisation of cis-4-ethoxycarbonylmethylidenebut-2-ene-4-olide (38)

The cis enol-lactone was similarly treated with sodium in absolute ethanol but isolation of the product yielded a dark oil and the n.m.r. spectrum indicated polymer formation.

Diethyl-3-ketoadipate (104)

The cis enol-lactone (53) (0.34 g, 0.002 mol) was added to sodium (0.07 g, 0.003 g atom) in absolute ethanol (10 ml) and the reaction mixture refluxed for seven hours. The ethanol was removed under reduced pressure and the residue dissolved in water and acidified with oxalic acid solution. The aqueous solution was extracted with ether, the ether extract washed with water and dried over anhydrous magnesium sulphate. Removal of the ether gave diethyl-3-ketoadipate (104) (0.4 g, 93%) which was distilled to give a colourless oil b.p. 108-110°/0.33 mm. (lit.[70] b.p. 109-111°/0.35 m.m.)

4-carboxyethyl-2,6-dihydroxypyrimidine (108)

The cis enol-lactone (53) (1.0 g, 0.006 mol) was added to a stirred solution of absolute ethanol (20 ml) containing sodium (0.27 g, 0.02 g atom) and urea (0.48 g, 0.008 mol). The reaction mixture was refluxed for seven hours and allowed to stand at room temperature for seven hours. The ethanol was removed under reduced pressure and

the residue dissolved in water and acidified with oxalic acid solution. Filtration gave the pyrimidine (108) (1.1 g, 91%) which was recrystallised from hot water to give colourless crystals m.p. 290-295° (with decomp.) (Found: C, 41.3; H, 4.97; N, 13.7. Calc. for $C_7H_7N_2O_4 \cdot H_2O$: C, 41.58; H, 4.99; N, 13.86%.) λ max 3400, 3500 (O-H), 1600-1700 cm^{-1} (C=O).

Reaction of diethyl-3-ketoadipate (104) with urea

The adipate was treated under identical conditions as the enol-lactone in the previous experiment and the pyrimidine (108) was again isolated. It was checked by mixed melting point (295-300°) and infrared spectrum and was found to be identical to the pyrimidine (108).

4-carboxyethyl-6-hydroxy-2-thiolpyrimidine (109)

The cis enol-lactone (53) was treated with thiourea under identical conditions as to its treatment with urea above. Filtration gave the thiolpyrimidine 92% which was recrystallised from hot water to give colourless crystals m.p. 230-240°. (Found: C, 37.8; H, 4.5; N, 12.7. Calc. for $C_7H_8N_2O_3S \cdot H_2O$: C, 38.5; H, 3.7; N, 12.8%.) λ max 3300-3500 (-OH), 1700 (C=O), 1640, 1630 cm^{-1} (C=O).

Attempted preparation of some other pyrimidines

The enol-lactones (2), (3), (44), (45), (46) and

(51) were all treated with sodium in ethanol and urea or thiourea as before but in all cases the cyclopent-4-ene-1,3-dione was isolated and characterized by mixed melting point.

Methylcarbonylmethylidene triphenylphosphorane (6)

The phosphonium salt, a colourless crystalline solid m.p. 232-234° (lit.[12] 234-237°) was prepared in 90% yield from chloroacetone and triphenylphosphine and converted to the phosphorane (6) (95%) according to the literature.[12] Recrystallisation from aqueous methanol gave a colourless crystalline solid m.p. 205-206° (lit.[12] 205-206°).

Chloromethylcarbonylmethylidene triphenylphosphorane (112)

The phosphonium salt was prepared according to Hudson and Chopard[71] in 80% yield and was precipitated from warm methanol with ethylacetate to give a colourless crystalline solid m.p. 208-211° (lit.[71] m.p. 210-212). The salt was converted to the phosphorane (90%) according to the literature[71] and drying in air gave colourless crystals m.p. 176-178° (lit.[71] m.p. 179-180°).

Ethylcarbonylmethylidene triphenylphosphorane (113)

Propionyl chloride (4.62 g, 0.05 mol) was treated with diazomethane[72] and hydrogen chloride according to the method of Catch et al[73] and gave 1-chloro-2-butanone

(4.0 g, 75%) which was distilled to give a colourless liquid b.p. 133-135° (lit.[74] b.p. 137°). The chlorobutanone (3.0 g, 0.028 mol) in benzene (20 ml) was added dropwise with stirring to triphenylphosphine (8.0 g, 0.032 mole) in benzene (20 ml) and the reaction mixture stirred for twelve hours at room temperature. The solution was filtered, the filtrate refluxed for one hour, cooled and filtered. The combined solids (10.0 g, 96%) were recrystallised from water and gave the phosphonium salt as a colourless crystalline solid m.p. 205-210°. The phosphonium salt (10.0 g, 0.027 mol) was dissolved in water (900 ml), filtered and cooled. Sodium hydroxide (1N) was added dropwise with vigorous stirring until a pale pink end-point with phenolphthalein indicated that the reaction mixture was alkaline. After maintaining the temperature at 0°C for one hour filtration gave the phosphorane (113) (8.5 g, 94%) which was recrystallised from ethylacetate/light petroleum as a colourless crystalline solid m.p. 221-222°. (Found: C, 79.1; H, 6.4. Calc. for $C_{22}H_{21}OP$: C, 79.5; H, 6.3%).

Isobutylcarbonylmethylidene triphenylphosphorane (47)

The phosphonium salt was prepared according to the method previously described[6] and converted to the phosphorane by titration[6] with sodium hydroxide (1N). Recrystallisation from light petroleum gave a colourless crystalline solid m.p. 120-122° (lit.[6] m.p. 120-122°).

t-butylcarbonylmethylidene triphenylphosphorane (41)

The phosphonium salt was prepared and converted to the phosphorane according to the method of Reynolds.[2] Recrystallisation from ethylacetate gave a colourless crystalline solid m.p. 174-176° (lit.[2] m.p. 175-177°).

Phenylcarbonylmethylidene triphenylphosphorane (50)

Phenacyl bromide was treated with triphenyl phosphine according to the method of Ramirez and Dershowitz[12] and the phosphonium salt was converted to the phosphorane according to the literature.[12] Drying in air gave a colourless crystalline solid m.p. 178-180° (lit.[12] m.p. 178-180°).

D_{15}-triphenylphosphine

D_5-phenyl lithium was prepared from d_5 bromobenzene according to the method of Evans and Allen[75] and then treated with phosphorous trichloride as described by Screttas and Isbell[76] to yield d_{15}-triphenylphosphine.

d_{15}-methylcarbonylmethylidene triphenylphosphorane (111)

The phosphorane was prepared in an identical manner to the unlabelled phosphorane (6) using d_{15}-triphenylphosphine.

d_{15}-phenylcarbonylmethylidene triphenylphosphorane (115)

This phosphorane was also prepared in an identical

manner to the unlabelled phosphorane (50) using d_{15}-triphenylphosphine.

d_1-phenylcarbonylmethylidene triphenylphosphorane (116)

The unlabelled phosphorane (50) (0.22 g) was dissolved in deuterium oxide (15 ml) and dimethylsulphoxide (5 ml), acidified with deuterium chloride and basified with sodium carbonate four times. The product was collected by filtration and washed with deuterium oxide (d_o = 12%, d_1 = 88%).

Ethoxycarbonylmethylidene triphenylphosphorane (34)

The phosphonium salt was prepared and converted to the phosphorane according to Isler et al.[77] Recrystallisation from ethylacetate/light petroleum gave a colourless crystalline solid m.p. 115-116° (lit.[77] m.p. 116-117°).

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