tinued for 6 more hours. The solution was cooled, acidified with dilute hydrochloric acid, and extracted with ether. The combined ether extract was washed to neutrality, dried over magnesium sulfate, and solvent was removed. Recrystallization of the crude product gave 0.300 g. of the dihydrooxadiazinone IIIa, m.p. 192–193° (70% yield).

Derivatives of Simple Ketones; Pinacolone Carbethoxyhydrazone.—Pinacolone (3.8 g., 0.038 mole) and carbethoxyhydrazine (4 g., 0.038 mole) were dissolved in 25 ml. of absolute ethanol containing 3 drops of glacial acetic acid. The solution was left to stand for 12 hr. at room temperature, after which time ethanol was removed *in vacuo* and the residue was taken up in 25 ml. of ether. On keeping in the cold, the derivative crystallized to give 3.5 g. of product, m.p. 85–86°.

Anal. Calcd. for $C_9H_{18}O_2N_2$: C, 58.06; H, 9.68; N, 15.05. Found: C, 58.05; H, 9.42; N, 15.03.

The carbethoxyhydrazone derivatives of acetone, m.p. 75–76°, and of benzophenone, m.p. 115–117° were similarly prepared.

Anal. Calcd. for $C_6H_{12}N_2O_2$: C, 50.00; H, 8.33; N, 19.44. Found: C, 50.38; H, 8.39; N, 18.89. Calcd. for $C_{16}H_{16}O_2N_2$: C, 71.64; H, 5.97; N, 10.45. Found: C, 71.55; H, 6.03; N, 10.31.

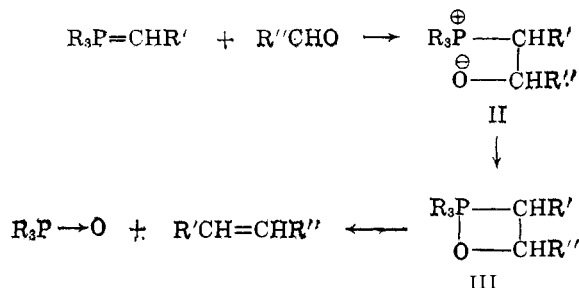# The Reactions of Phosphorus Compounds. VIII. Kinetics and Mechanism of the Wittig Reaction

BY A. J. SPEZIALE AND D. E. BISSING
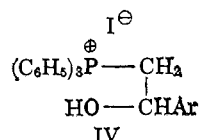
The rates of reaction of carbomethoxymethylenetriphenylphosphorane with a series of aromatic aldehydes have been studied in benzene, chloroform, and methanol. The reaction is cleanly second order, first order in each of ylid and aldehyde. The reaction rate is increased by increasing solvent polarity, by substitution of butyl for phenyl on phosphorus in the ylid, and by electron-withdrawing substituents in the aldehyde. The slope of the $\rho\sigma$ plot is +2.7. The reversibility of betaine formation in the Wittig reaction of stable ylids has been demonstrated by trapping the ylid formed by decomposition of the betaine derived from reaction of a phosphine with an epoxide. A mechanism for the Wittig reaction of stable ylids is proposed and substantiated.

Although the synthetic applications of the Wittig reaction are well known,[1,2] a detailed mechanistic study has not been reported. Investigations from these laboratories[3,4] as well as others[5–8] have treated this reaction in qualitative terms. We wish now to amplify our recent communication[9] of the kinetics, stereochemistry, and mechanism of the Wittig reaction.

$$R_3P{=}CHR' \ + \ R''CHO \ \longrightarrow \ \overset{\oplus}{R_3P}{-}\!\!\begin{array}{c}CHR'\\|\\ \end{array}$$
$$\overset{\ominus}{O}{-}CHR''$$
$$\mathrm{II}$$

$$\downarrow$$

$$R_3P{\rightarrow}O \ + \ R'CH{=}CHR'' \ \longleftarrow \ \begin{array}{cc}R_3P&{-}CHR'\\|&|\\O&{-}CHR''\end{array}$$
$$\mathrm{III}$$

The importance of II and/or III has not been definitely established although their existence has been demonstrated by the isolation of IV from reaction of II or III (R = C_6H_5, R' = H, R'' = Ar) with hydrogen iodide.[5]

$$\overset{\mathrm{I}^{\ominus}}{\underset{\mathrm{IV}}{\overset{\oplus}{(C_6H_5)_3P}{-}\!\!\begin{array}{c}CH_2\\|\\HO{-}CHAr\end{array}}}$$

Since IV, on heating, gave triphenylphosphine oxide and styrene and only trace amounts of 1,1-diphenylethylene in the presence of benzophenone, irreversible formation of the betaine II was postulated.[5]

In the reaction of the stable triphenyl- and tributylphosphonium fluoreneylids with carbonyl compounds, the betaine intermediate could not be trapped by quenching the reaction with acid.[6a,b] In each case, only the phosphonium salt derived from the starting ylid was isolated. The tributyl ylids furnished much better yields of olefin than did the triphenyl ylids under similar reaction conditions. These data provided evidence for an inherent difference in the mechanistic path for reaction of stable and unstable ylids.[10]

Stable ylids, in their reactions with carbonyl compounds, gave predominantly the *trans*-olefins,[4,11,12] while unstable ylids yielded mixtures of the two possible stereoisomers.[13,14] In an attempt to explain the stereoselectivity of the reaction of methylcarbomethoxymethylenetriphenylphosphorane with acetaldehyde, House and Rasmusson[7] postulated that steric interactions between ylid and aldehyde in the formation of the betaine intermediate were not sufficient to account for the observed product ratio (96.5% methyl tiglate and 3.5% methyl angelate). They proposed instead a mechanism involving rapid, reversible formation of two stereoisomeric betaines, one of which decomposes to olefin and phosphine oxide faster than the other. The transition state for decomposition of the betaine leading to *trans*-olefin would be stabilized by overlap of the π-orbitals of the carbomethoxy group with those of the incipient double bond, while steric interactions between the carbomethoxy group and the eclipsed methyl group would prohibit similar stabilization of the transition

(1) (a) J. Levisalles, *Bull. soc. chim. France*, 1021 (1958); (b) G. Wittig and V. Schollkopf, *Ber.*, **87**, 1318 (1954).

(2) S. Trippett, "Advances in Organic Chemistry," Vol. I, Interscience Publishers, Inc., New York, N. Y., 1960, pp. 83–102.

(3) A. J. Speziale and K. W. Ratts, *J. Org. Chem.*, **28**, 465 (1963).

(4) A. J. Speziale and K. W. Ratts, *J. Am. Chem. Soc.*, **85**, 2790 (1963).

(5) G. Wittig, H. Weizmann, and M. Schlosser, *Ber.*, **94**, 676 (1961).

(6) (a) A. W. Johnson and R. B. LaCount, *Tetrahedron*, **9**, 130 (1960); (b) A. W. Johnson and R. B. LaCount, *Chem. Ind.* (London), 52 (1959).

(7) H. O. House and G. H. Rasmusson, *J. Org. Chem.*, **26**, 4278 (1961).

(8) H. J. Bestmann and O. Kratzer, *Ber.*, **95**, 1894 (1962).

(9) A. J. Speziale and D. E. Bissing, *J. Am. Chem. Soc.*, **85**, 1888 (1963).

(10) The term "unstable ylid," in general, refers to those ylids which are nonisolable, while "stable ylids" refers to those ylids which are isolable and contain a group through which the negative charge at carbon may be delocalized. Differentiation between stable and unstable ylids is not clear-cut and between these two extremes lie a series of compounds which show some of the chemical properties of each.

(11) R. Ketcham, D. Jambotkar, and L. Martinelli, *J. Org. Chem.*, **27**, 4666 (1962).

(12) V. Schollkopf, *Angew. Chem.*, **71**, 260 (1959).

(13) (a) L. D. Bergelson, V. Vaver, L. Barsukov, and M. M. Shemyakin, *Dokl. Akad. Nauk S.S.S.R.*, **143**, 111 (1962); (b) L. D. Bergelson, V. Vaver, and M. M. Shemyakin, *Izvest. Akad. Nauk S.S.S.R., Otd. Khim. Nauk*, 729 (1961).

(14) A. Blade-Font, C. A. VanderWerf, and W. E. McEwen, *J. Am. Chem. Soc.*, **82**, 2396 (1960).

TABLE I

Reaction of $(C_6H_5)_3P{=}CCO_2CH_3$ +

Y (attached), CHO—X (phenyl ring)

X	Y	Temp. $\pm 0.05°$	Solvent	$k_{obsd} \times 10^4$, l./mole-sec.	E_a, kcal./mole	ΔS^*, e.u., 25°
p-CH₃O	H	25.0	Benzene	0.710 ± 0.000	11.3	−41.6
		45.0	Benzene	2.36 ± .02		
		25.0	Chloroform	4.35 ± .02		
		25.0	Methanol	657.0 ± 3.0		
p-CH₃	H	25.0	Benzene	2.15 ± .03	10.7	−41.6
		45.0	Benzene	6.69 ± .04		
		25.0	Chloroform	12.4 ± .30		
p-H	H	25.0	Benzene	9.62 ± .02	10.2	−40.3
		45.0	Benzene	28.6 ± .4		
		25.0	Chloroform	43.6 ± .4		
	Cl	25.0	Benzene	5.75 ± .02		
	Br	25.0	Benzene	1.85 ± .01		
p-Cl	H	25.0	Benzene	24.5 ± .0	9.5	−40.6
		45.0	Benzene	67.1 ± .3		
		25.0	Chloroform	124 ± 1.0		
m-Cl	H	25.0	Benzene	120 ± 4.0		
p-NO₂	H	25.0	Benzene	1060 ± 0.0		

state for decomposition of the betaine leading to *cis*-olefin.

Bestmann and Kratzer[8] reported that reaction of tricyclohexylphosphinealkylenes with carbonyl compounds afforded a greater predominance of the *trans*-olefin than did the corresponding triphenylphosphinealkylenes. A mechanism similar to that proposed by House was postulated. The cyclohexyl groups, being more electron donating than phenyl, would retard the decomposition of the betaine, thereby effecting complete equilibration between the two stereoisomeric betaines.

It was observed in these laboratories[4] that competition reactions of a single ylid with two aldehydes of differing reactivity, *e.g.*, benzaldehyde and *p*-nitrobenzaldehyde, always resulted in the exclusive formation of that olefin derived from the most reactive aldehyde (*p*-nitrobenzaldehyde). These results are inconsistent with a mechanism involving rapidly reversible betaine formation and rate-determining decomposition of the betaine. Although the betaine would be formed more rapidly from *p*-nitrobenzaldehyde, the *p*-nitro group would undoubtedly retard the decomposition of the betaine. Hence, it seemed likely that the rate-determining step must involve nucleophilic attack of ylid upon aldehyde and that the stereospecificity of the Wittig reaction of stable ylids could indeed be explained by differing steric interactions between ylid and aldehyde in the formation of the stereoisomeric betaines leading to *cis*- and *trans*-olefins.

Results

Kinetics.—The rate of disappearance of carbomethoxymethylenetriphenylphosphorane in its reaction with a series of *m*- and *p*-substituted benzaldehydes in benzene, chloroform, and methanol was measured at 25 and 45° by potentiometric titration of the ylid with aqueous acid.[4] The reaction was cleanly second order; first order in each of aldehyde and ylid. Second-order rate constants obtained from the slopes of plots of $1/C_t$ or log (A_0B_t/B_0A_t) *vs.* time are given in Table I. These plots were linear to at least 80% of reaction. Activation parameters calculated for those compounds whose rates were studied at two temperatures are also included. A plot of the kinetic data obtained in benzene at 25° *vs.* σ (Fig. 1) was linear with slope +2.7.

In addition to the kinetic data reported in Table I, a single study of the rate of reaction of carbethoxymethyl-

enetributylphosphorane with *p*-methoxybenzaldehyde was performed in benzene at 25° (k_{obsd} = 5.61 × 10⁻³ l./mole-sec.). The absolute value of this rate constant is in doubt since the ylid was prepared from the phosphonium bromide and butyllithium and used *in situ*. The resulting solution, therefore, contained a small amount of hexane and a stoichiometric amount of lithium bromide.
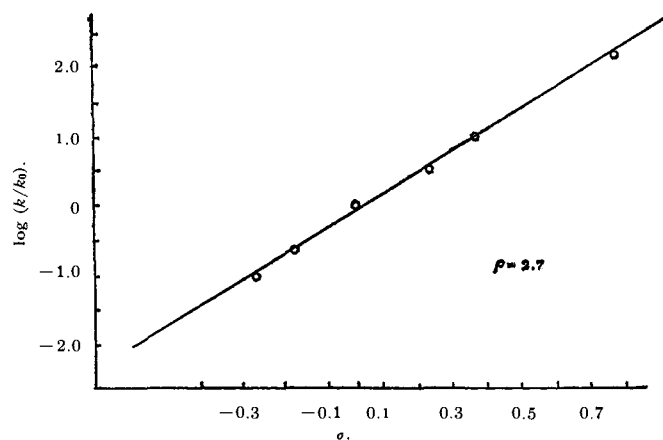
Figure 1.

In the reaction of carbomethoxymethylenetriphenylphosphorane with *p*-methoxybenzaldehyde the rate of olefin formation was followed in benzene at 25° by a bromometric method. The rate constant thus derived was 7.00 ± 0.13 × 10⁻⁵ l./mole-sec. Within experimental error the rate of formation of olefin was the same as the rate of disappearance of the ylid.

Ring Opening of Epoxides with Phosphines.—In order to establish the reversibility or irreversibility of betaine formation in the Wittig reaction, the reactions of tributyl- and triphenylphosphine with *cis*- and *trans*-ethyl phenylglycidate, in the presence of *m*-chlorobenzaldehyde, were examined in refluxing ethanol. If betaine formation were reversible, the ylid should be trapped by the more reactive *m*-chlorobenzaldehyde. The products from these reactions were analyzed by v.p.c. In one case the products were isolated by preparative v.p.c. and identified as described in the Experimental section. The results of these experiments with tributylphosphine and triphenylphosphine are re-

$$R_3P{\rightarrow}O + C_6H_5CH{=}CHCO_2C_2H_5$$

$$\uparrow$$

$$R_3P + C_6H_5\overset{O}{\overset{\diagdown}{CH}}{-}CHCO_2C_2H_5 \rightarrow R_3\overset{\oplus}{P}{-}\overset{|}{C}HCO_2C_2H_5$$
$$\overset{\ominus}{O}{-}\overset{|}{C}HC_6H_5$$

$$R_3P{=}CHCO_2C_2H_5 + C_6H_5CHO \xrightarrow{m\text{-}ClC_6H_4CHO}$$

$$R_3P{\rightarrow}O$$
$$+$$
$$CH{=}CHCO_2C_2H_5$$

a, R = C_6H_5; b, R = C_4H_9

ported in Table II. The reactions of the *cis*- and *trans*-epoxides with tributyl- and triphenylphosphine were also studied in the absence of *m*-chlorobenzaldehyde in order to establish their stereochemistry. These results are reported in Table III.

TABLE II

$$\overset{O}{\overset{\diagup\diagdown}{}}$$
REACTION OF R_3P (a) + $C_6H_5CH{-}CHCO_2C_2H_5$ (b) +
m-ClC_6H_4CHO (c)

			Product olefins, mole %			
		Rel. concn.	$C_6H_5CH{=}$ $CHCO_2C_2H_5$		*m*-$ClC_6H_4CH{=}$ $CHCO_2C_2H_5$	
R	Epoxide	(a:b:c)	cis	trans	cis	trans
C_4H_9	trans	1:1:3	0	53.2	0	46.8
C_4H_9	trans	1:1:1	0	53.6	0	46.4
C_4H_9	cis	1:1:3	0	92.4	0	7.6
C_6H_5	trans	1:1:3	49.1	17.4	3.0	30.5
C_6H_5	trans	1:1:1	48.7	17.4	3.0	30.9
C_6H_5	cis	1:1:3	1.2	85.8	1.2	11.8

TABLE III

$$\overset{O}{\overset{\diagup\diagdown}{}}$$
REACTION OF R_3P + $C_6H_5CH{-}CHCO_2C_2H_5$
(EQUIMOLAR AMOUNTS)

		$C_6H_5CH{=}CHCO_2C_2H_5$, mole %	
R	Epoxide	cis	trans
C_4H_9	trans	0	100
C_4H_9	cis	0	100
C_6H_5	trans	41.3	58.7
C_6H_5	cis	3.0	97.0

The data in Tables II and III show the total absence of *cis*-ethyl cinnamate when tributylphosphine was used. The relative proportions of olefins are difficult to explain even in the reactions involving triphenylphosphine. It seemed likely that the stereochemistry of the reaction was being influenced by factors other than the normal Wittig path. Consequently, the stereochemical stability of *cis*-ethyl cinnamate in the presence of several of the reactants, intermediates, and products was determined under the conditions of the ring opening reaction of the epoxides. *cis*-Ethyl cinnamate was not isomerized by carbethoxymethylenetributylphosphorane, carbethoxymethylenetriphenylphosphorane, tributylphosphine oxide, or triphenylphosphine oxide. However, significant isomerization was effected by tributylphosphine and triphenylphosphine. *cis*-Ethyl cinnamate was completely isomerized to *trans*-ethyl cinnamate by tributylphosphine after 20 hr. in refluxing ethanol, whereas with triphenylphosphine the isomerization was 60% complete after 5 days in refluxing ethanol. *trans*-Ethyl cinnamate was not affected under the same conditions.

Competition Experiments and Stereochemistry of the Wittig Reaction.

—In order to place the data obtained from the epoxide reaction on a more quantitative basis, the stereochemistry of the reaction of carbethoxymethylenetriphenylphosphorane with benzaldehyde and *m*-chlorobenzaldehyde as well as the reaction of carbethoxymethylenetributylphosphorane with benzaldehyde in refluxing ethanol were studied. In addition, competition experiments of carbethoxymethylenetriphenylphosphorane with benzaldehyde and *m*-chlorobenzaldehyde were performed so that product ratios would be available. The results of these experiments are shown in Tables IV and V.

TABLE IV

REACTION OF $R_3P{=}CHCO_2C_2H_5$ +
$$\overset{CHO}{\underset{X}{\bigcirc}}$$

		Olefins, mole %	
X	R	cis	trans
p-H	C_4H_9	5	95
p-H	C_6H_5	16	84
m-Cl	C_6H_5	12	88

TABLE V

REACTION OF $(C_6H_5)_3P{=}CHCO_2C_2H_5$ (a) + C_6H_5CHO (b) +
m-ClC_6H_4CHO (c)

Rel. concn.	$C_6H_5CH{=}CHCO_2C_2H_5$		*m*-$ClC_6H_4CH{=}CHCO_2C_2H_5$	
(a:b:c)	cis	trans	cis	trans
1:1:1	3.2	22.4	9.2	65.2
1:1:3	0.7	5.7	13.2	80.4

Discussion of Results

At the outset of this work, four distinct mechanisms for the Wittig reaction of stable ylids were considered: (a) rapid, irreversible betaine formation and its rate-controlling decomposition to products; (b) slow, irreversible formation of betaine and rapid decomposition of betaine to products; (c) rapid, reversible betaine formation and rate-determining formation of phosphine oxide and olefin; (d) slow, reversible betaine formation with rapid decomposition of betaine to phosphine oxide and olefin. Mechanism a is not likely since there is no reason to expect that betaine formation would be irreversible if its decomposition to products were rate controlling.

On the basis of the ring opening reaction of *trans*-ethyl phenylglycidate with tributyl- and triphenylphosphines, mechanisms a and b can be eliminated. The incorporation of *m*-chlorobenzaldehyde in these reactions conclusively demonstrates that betaine formation is reversible. Mechanisms c and d, represented by the following mechanistic scheme, differ in the relative values of the rate constants, k_1, k_{-1}, and k_2.

$$(C_6H_5)_3P{=}CHCO_2CH_3 \underset{+}{\overset{k_1}{\underset{k_{-1}}{\rightleftharpoons}}} (C_6H_5)_3\overset{\oplus}{P}{-}\overset{|}{C}HCO_2CH_3 \xrightarrow{k_2}$$
$$C_6H_5CHO \qquad \overset{\ominus}{O}{-}\overset{|}{C}HC_6H_5$$
$$(C_6H_5)_3P{\rightarrow}O + (C_6H_5)CH{=}CHCO_2CH_3$$

Derivation of the rate expression by invoking the steady-state approximation for the intermediate betaine yields

$$\frac{-d[(C_6H_5)_3P{=}CHCO_2CH_3]}{dt} =$$
$$\frac{k_1k_2}{k_{-1} + k_2}[(C_6H_5)_3P{=}CHCO_2CH_3][C_6H_5CHO] \quad (1)$$

Mechanism c implies $k_{-1} \gg k_2$ and eq. 1 becomes

$$\frac{-d[(C_6H_5)_3P{=}CHCO_2CH_3]}{dt} =$$
$$Kk_2[(C_6H_5)_3P{=}CHCO_2CH_3][C_6H_5CHO] \quad (2)$$

K is the equilibrium constant for betaine formation. Mechanism d arises when k_{-1} and k_2 are of the same order of magnitude or $k_{-1} = nk_2$ where n is a small constant. Equation 1 then reduces to

$$\frac{-d[(C_6H_5)_3P\!=\!CHCO_2CH_3]}{dt} =$$

$$\frac{k_1}{n+1}\ [(C_6H_5)_3P\!=\!CHCO_2CH_3][C_6H_5CHO]\ ^{16}\quad(3)$$

If mechanism c is operative, a positive value of ρ would be predicted for the equilibrium step (betaine formation), for this step involves addition of the ylid to the carbonyl group.[16] Assuming that V represents the transition state, a negative value of ρ would be predicted for betaine decomposition. The net effect of

$$(C_6H_5)_3\overset{\delta\oplus}{P}\text{-----}\overset{\delta\ominus}{C}HCO_2C_2H_5$$
$$\overset{\delta\ominus}{O}\text{-----}\overset{\delta\oplus}{C}HC_6H_5$$
$$V$$
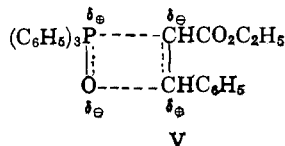
p-substitution would be rather small and of unpredictable sign. The observed ρ value of $+2.7$ is too large to be consistent with mechanism c. Furthermore, the rate effects observed with halo ylids and phenyl and butyl ylids rule out mechanism c. Halogen should diminish the nucleophilicity of the ylid, the result being a decrease in K. The same substitution would increase the stability of the transition state for betaine decomposition by inductive stabilization of the incipient negative charge at the carbon α to phosphorus in V and thereby enhance k_2. Therefore, if betaine decomposition is rate controlling, the halogen-substituted ylid would react faster than the parent hydrogen ylid. The halogenated compounds, however, react slower than the parent ylids. It should be mentioned, however, that steric effects undoubtedly play a role in the observed rate decrease with the halo ylids. A discussion of these factors may be found elsewhere.[4] The substitution of butyl for phenyl in the ylid would enhance the nucleophilicity of the ylid and K would increase. The same substitution, however, would diminish k_2 since the greater electron-donating capacity of butyl would retard the closure of the four-membered ring. The tributyl ylid reacts about eighty times faster than the triphenyl ylid.

Equation 3 derived for mechanism d involves a single rate constant, that for betaine formation (k_1). All of the kinetic data are consistent with this mechanism. The effect of substitution in the aldehyde should parallel the effects observed in other carbonyl addition reactions. The observed ρ value of 2.7 is in good agreement with similar reactions.[17,18] Likewise, the sub-

stitution of α-halogen in the ylid would be expected to cause a decrease in k_1 and the substitution of butyl for phenyl at phosphorus would be expected to effect an increase in k_1. All of these effects were observed.

The effect of solvent polarity upon the reaction rates is also mechanistically indicative. The reaction of ylid and aldehyde is 5–6 times faster in chloroform than in benzene and about 1000 times faster in anhydrous methanol than in benzene. Since charge is being formed during betaine formation and destroyed thereafter, the observed rate increase with increasing solvent polarity is consistent with mechanism d, though perhaps not entirely inconsistent with mechanism c.

The ring opening of cis- and trans-ethyl phenylglycidate with phosphines also furnishes evidence for mechanism d rather than mechanism c. The attack of tertiary phosphines on cis- and trans-2-butene oxides[19] and of triisopropyl phosphite on ethylene oxide[20] occur mainly at carbon. Furthermore, nucleophilic attack on ethyl phenylglycidate takes place predominantly at the carbon atom α to the carbethoxy group.[21] The reaction of tributylphosphine or triphenylphosphine with trans-ethyl phenylglycidate (VI) affords initially the betaine intermediate VII which collapses to cis-ethyl cinnamate. Conversely, the opening of cis-ethyl phenylglycidate (VIII) with phosphines gives the betaine intermediate IX, which leads to trans-ethyl cinnamate.[22]

a, R = C_6H_5;   b, R = C_4H_9
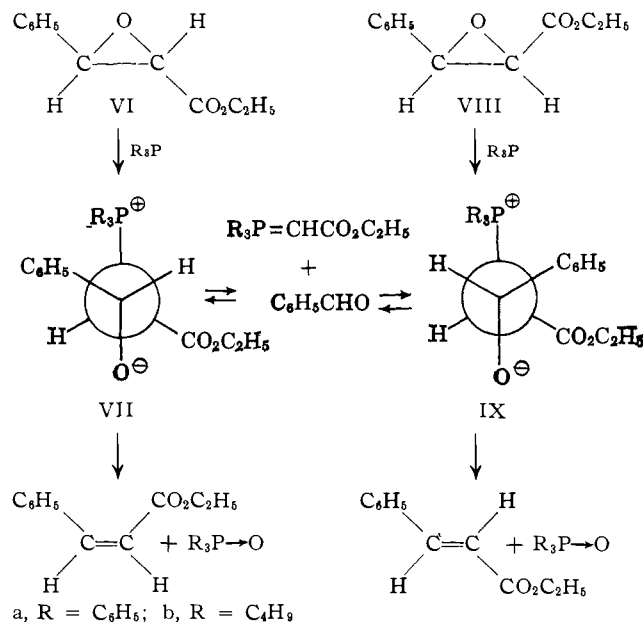
An additional source of trans-ethyl cinnamate in the first case and cis-ethyl cinnamate in the latter case may arise by direct deoxygenation of the epoxides by the phosphine. This path does not require the intermediacy of the betaine.

(15) The over-all rate for mechanism d actually depends not only upon k_1 but also upon the partitioning of the betaine intermediate (k_{-1}/k_2). However, changes in k_1, effected by substitution in the aldehyde or ylid, are much more important in determining the over-all rate than are changes in k_{-1}/k_2 caused by the same substitution. Consequently, the substitution of "n" for k_{-1}/k_2 to yield eq. 3 is valid if it is understood that the value of "n" depends upon aldehyde and ylid substitution. For a similar conclusion see: S. J. Rhoads and R. Michel, J. Am. Chem. Soc., 85, 585 (1963).

(16) In a recent paper, Bergelson and Shemyakin [(Tetrahedron, 19, 149 (1963)] have proposed that the initial step of the Wittig reaction of stable ylids involves irreversible nucleophilic attack of the carbonyl oxygen upon phosphorus. It is possible to explain the stereospecificity observed in this reaction without invoking this tenuous explanation. For example, we have shown that betaine formation is reversible and their explanation was based upon the assumption of irreversible betaine formation. Furthermore, if their postulate is correct, competition experiments between a single ylid and two aldehydes of differing reactivity should result in predominant formation of the olefin derived from the aldehyde whose carbonyl oxygen is most nucleophilic. In fact, our competition experiments show that such experiments yield the olefin derived from the aldehyde whose carbonyl carbon is most electrophilic (Table V). There are also other arguments which refute the proposal of the Russian workers equally well.

(17) (a) D. P. Evans, J. J. Gordon, and H. B. Wilson, J. Chem. Soc., 722 (1937); (b) C. K. Ingold and W. S. Nathan, ibid., 1430 (1937).

(18) E. Tommilla, Ann. Acad. Sci. Fennicae, 459, N.8 (1942).
(19) D. B. Denney and M. J. Boskin, Chem. Ind. (London), 330 (1959).
(20) C. B. Scott, J. Org. Chem., 22, 1118 (1957).
(21) R. E. Parker and N. S. Isaacs, Chem. Rev. 59, 737 (1959).
(22) Our treatment of the data obtained from the opening of the epoxides is based upon the assumption, with adequate precedent, that attack of the phosphine occurs at the carbon atom adjacent to the carbethoxy group. Unequivocal proof that phosphine is not also attacking the carbon atom adjacent to the phenyl group is unavailable at this time. However, no m-chlorostilbene was observed in any of our experiments. If attack at the β-carbon atom is occurring, it must be assumed that only the betaine arising from attack of phosphine at the α-carbon decomposes to ylid and aldehyde. Treatment of trans-stilbene oxide with triphenyl- and tributylphosphines in the presence of excess m-chlorobenzaldehyde resulted in the formation of significant amounts of m-chlorostilbene. Furthermore, kinetic studies have shown that trans-ethyl phenylglycidate is opened by triphenylphosphine about ten times as fast as trans-stilbene oxide. These data certainly support our contention that attack by phosphine is occurring at the α-carbon atom.

$$R_3P + C_6H_5CH \overset{O}{\overbrace{}} CHCO_2C_2H_5 \longrightarrow$$

$$R_3P\text{-----}\overset{.}{O} \begin{matrix} CHCO_2C_2H_5 \\ | \\ CHC_6H_5 \end{matrix} \longrightarrow R_3P{\rightarrow}O + C_6H_5CH{=}CHCO_2C_2H_5$$

It is quite likely that the rate-determining step in the epoxide ring opening reaction is the attack of phosphine at the α-carbon atom. Subsequent steps are almost certainly rapid. Consequently, the initial relative concentrations of phosphine, epoxide, and m-chlorobenzaldehyde do not reflect the actual reaction course. The concentration of m-chlorobenzaldehyde is far greater than that of the ylid or benzaldehyde at any time during the reaction. The data reported in Tables II and III support this contention. The initial concentration of m-chlorobenzaldehyde has no effect upon the relative amounts of ethyl cinnamate and ethyl m-chlorocinnamate formed. All of the ylid formed by decomposition of the betaine, therefore, reacts with m-chlorobenzaldehyde, and hence all of the ethyl cinnamate arises either by direct reaction of the betaine or the side reaction mentioned previously.

A semiquantitative evaluation of the amount of direct deoxygenation of the epoxide by triphenylphosphine is possible from the data reported in Tables II, III, and IV. In the reaction of the $trans$-epoxide with triphenylphosphine, in the absence of m-chlorobenzaldehyde (Table III), approximately 60% of the olefin mixture was $trans$. About 34% of the betaine, once formed, decomposes to ylid and aldehyde (sum of the cis- and $trans$-ethyl m-chlorocinnamates, Table II). Therefore, in the subsequent reaction of ylid and aldehyde approximately 85% of the resulting olefin should be $trans$ (product ratios, Table IV). This accounts for half of the observed 60% $trans$-olefin. It was also previously mentioned that the cis-olefin is isomerized by triphenylphosphine. The remaining half of the 60% $trans$-olefin can be accounted for by isomerization of the cis-olefin formed by direct decomposition of the betaine. Similarly, in the reaction of triphenylphosphine with the cis-epoxide only 3% of the cis-olefin is observed (Table III), and 13% of the betaine, once formed, decomposes to ylid and aldehyde (sum of cis- and $trans$-ethyl m-chlorocinnamates, Table II). In the subsequent reaction of ylid and aldehyde 85% of the resulting olefin would be $trans$, thus leaving a calculated amount of 2% cis-olefin for the entire reaction.

The agreement between calculated and observed product ratios for the cis-epoxide is better than for the $trans$-epoxide. This is not surprising since direct decomposition of the betaine derived from cis-epoxide yields $trans$-olefin which is not isomerized by phosphine. Reaction of the ylid and aldehyde derived from this betaine also yields $trans$-olefin as the predominant product. Therefore, isomerization of the olefin by phosphine is by no means as important as it is in the reaction of the $trans$-epoxide which initially yields cis-olefin as its direct decomposition product. In both cases the agreement is surprisingly good and, although no direct proof exists, it is not illogical to assume that the direct deoxygenation of either epoxide by phosphine is negligible.

The difference in the amount of incorporation of m-chlorobenzaldehyde in the ring opening of the cis- and $trans$-epoxides is rather striking (Tables II and III). If all of the reaction proceeds via the betaine intermediate, the more sterically hindered cis-betaine derived from the $trans$-epoxide would decompose with about equal ease to phosphine oxide and olefin and to ylid and aldehyde

when tributylphosphine is used. When triphenylphosphine is the nucleophile, the decomposition of betaine to phosphine oxide and olefin is favored over its decomposition to ylid and aldehyde by a factor of 2:1. With tributylphosphine the sterically more favorable $trans$-betaine, derived from the cis-epoxide, decomposes about 15 times as fast to olefin and phosphine oxide than to ylid and aldehyde, and about 7 times as fast when triphenylphosphine is the nucleophile.

Disregarding the stereochemistry of the olefin obtained in the reaction of the cis- and $trans$-epoxides with the two phosphines for the moment, it is possible to discard mechanism c on the basis of relative amounts of the substituted and unsubstituted olefins obtained. If mechanism c were operative and betaine formation were rapidly reversible, there should be obtained no more (and probably much less) ethyl cinnamate than in the competition experiments listed in Table VI. However, with both epoxides more ethyl cinnamate was observed than ethyl m-chlorocinnamate. This evidence, as well as the observed substituent effects upon the rates of the reaction, suggests the following mechanism for the Wittig reaction of stable ylids.

$$(C_6H_5)_3P{=}CHCO_2CH_3 + C_6H_5CHO$$

In terms of the broad mechanistic picture, all of the data strongly suggest that the rate of formation of betaine is less than its rate of decomposition via either of the two alternate paths.

The potential energy profile for this mechanism is shown in Fig. 2.

From the data in Table II, the values of k_{-1}/k_2 for the various reactions can be calculated. These are shown in Table VI.

TABLE VI

RATIO OF RATE CONSTANTS FOR BETAINE DECOMPOSITION

R	Epoxide	k_{-1}/k_2
C_4H_9	$trans$	0.87
C_4H_9	cis	.082
C_6H_5	$trans$	.50
C_6H_5	cis	.15

It is more reasonable to discuss the mechanism in terms of the relative values of the various rate constants rather than in terms of a single rate-determining step. The calculated values of k_{-1}/k_2 as shown in Table VII are quite illuminating.

The $trans$-betaine (derived from cis-epoxide) decomposes to $trans$-olefin and phosphine oxide 6.7 times faster than it decomposes to ylid and aldehyde, while the cis-betaine (derived from $trans$-epoxide) decomposes to cis-olefin and phosphine oxide only twice as fast as it does to ylid and aldehyde. These ratios almost certainly reflect differences in both k_{-1} and k_2 for the cis- and $trans$-betaines. However, if it is assumed that $k_{-1}{}^c$ and $k_{-1}{}^t$ do not differ significantly, then $k_2{}^t =$

$3.5k_2{}^c$. Furthermore, if the two stereoisomeric betaines are formed at the same rate in the normal Wittig reaction, the difference between $k_2{}^t$ and $k_2{}^c$ would predict that the *trans*-olefin should predominate by about 4:1. The observed value is 5:1 (Table V). Ylid and aldehyde therefore react to form *trans*-betaine faster than *cis*-betaine; e.g., $k_1{}^t > k_1{}^c$. Inspection of models shows that steric interactions for the formation of *cis*-betaine are greater than those for formation of *trans*-betaine if the phosphorus and the carbonyl oxygen are eclipsed during the formation of both betaines.

The stereochemistry of the Wittig reaction is therefore controlled primarily by the relative rates of decomposition of the two stereoisomeric betaines, thus lending direct support to House's proposal.[7] However, the two betaines are formed at significantly different rates so that betaine formation also plays a part in the over-all stereochemistry of the reaction.

The data obtained in the reaction of tributylphosphine with the *cis*- and *trans*-epoxides indicate that the same factors mentioned above are operative. Although $k_{-1}{}^c \cong k_2{}^c$, $k_2{}^t > k_{-1}{}^t$ by an amount larger than the corresponding difference in the triphenyl case (Table VI). The explanation for this difference lies in the fact that the electron-donating capabilities of butyl render the ring closure of the betaine more difficult. More importance must therefore be placed upon the stabilization of the transition state leading to *trans*-olefin by coplanarity of the carbomethoxy group and the developing double bond. This explanation may be used to explain the observed fact that tricyclohexyl ylids[8] and our own tributyl ylid react with benzaldehyde to give a greater predominance of *trans*-olefin than do the triphenyl ylids.

The reactions of carbomethoxymethylenetriphenylphosphorane with aromatic aldehydes show surprisingly small activation energies and large negative entropies of activation (Table I). Cox[23] observed that the reaction of phenacyl bromide and aniline in benzene possessed a low activation energy and a large negative activation entropy. The activation parameters observed in the Wittig reaction are therefore not without precedence in other reactions involving polar transition states. The large negative activation entropies can be attributed to several factors. Betaine formation in benzene involves charge localization in a nonpolar solvent and this in itself would require negative activation entropy. However, it is likely that the transition state for betaine formation is highly oriented, the incipient positive charge at phosphorus and the developing negative charge at oxygen being eclipsed (X).

$$(C_6H_5)_3\overset{\oplus}{P} \qquad \overset{\ominus}{O}$$

X
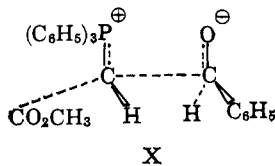
The activation parameters were calculated from data obtained at only two temperatures and there is no assurance that activation energy is temperature independent. Since the reaction involves partitioning of an intermediate, it is possible that activation energy will show temperature dependence.[24]

A study of the temperature dependence of activation energy and of the values of k_{-1}/k_2 will give further insight into the mechanism of the Wittig reaction. If it is found that activation energy is temperature inde-

(23) H. E. Cox, *J. Chem. Soc.*, 142 (1921).
(24) A. Weissberger, "Techniques of Organic Chemistry," Vol. VIII, Part II, Interscience Publishers, Inc., New York, N. Y., pp. 1427–1431.
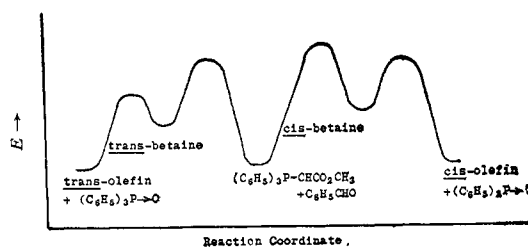
Figure 2.

pendent as for ester and amide hydrolysis,[25] the available values of k_{-1}/k_2 will lend themselves to calculation of the differences in activation energies for the two possible decomposition pathways for the betaines, e.g., to ylid and aldehyde and to phosphine oxide and olefin.

Finally, the generality of mechanism d in the reaction of stable ylids with carbonyl compounds remains to be proven. It is possible that other ylids, under various reaction conditions, will exhibit changes in k_1, k_{-1}, and k_2 sufficient to cause the intervention of mechanisms b or c. Further work in this area is desirable and such a study is currently under way in these laboratories.

Experimental[26]

Materials.—All aldehydes were purchased and twice distilled prior to use. *trans*-Ethyl phenylglycidate was obtained from Dodge and Olcott, Inc. Tributylphosphine, obtained from FMC Corp., was distilled prior to use. Triphenylphosphine, obtained from Metal Thermit, Inc., was recrystallized from hexane.

Carbomethoxymethyltriphenylphosphonium bromide was prepared according to the procedure of Isler[27]; m.p. 167–170° (reported[27] m.p. 163°).

Carbomethoxymethylenetriphenylphosphorane was prepared according to the procedure of Ratts and Speziale[3]; m.p. 168–169° (reported[27] m.p. 162–163°).

Anal. Calcd. for $C_{21}H_{19}O_2P$: C, 75.43; H, 5.73; P, 9.26. Found: C, 75.57; H, 5.73; P, 9.27.

Bromocarbomethoxymethylenetriphenylphosphorane was synthesized according to the procedure of Ratts and Speziale[3]; m.p. 163–164° dec.

Anal. Calcd. for $C_{21}H_{18}BrO_2P$: C, 61.03; H, 4.39; Br, 19.34; P, 7.50. Found: C, 61.04; H, 4.41; Br, 19.36; P, 7.46.

Chlorocarbomethoxymethylenetriphenylphosphorane was prepared according to the procedure of Ratts and Speziale[3]; m.p. 171.5° dec.

Anal. Calcd. for $C_{21}H_{18}ClO_2P$: C, 68.39; H, 4.92; Cl, 9.61; P, 8.40. Found: C, 68.29; H, 4.96; Cl, 9.73; P, 8.44.

Carbethoxymethyltributylphosphonium Bromide.—One hundred grams (0.5 mole) of tributyl phosphine was dissolved in 300 ml. of benzene and 83 g. (0.5 mole) of ethyl bromoacetate was added dropwise over a 30-min. period. The solution was refluxed for 2 hr., cooled, and solvent removed *in vacuo*, leaving a nearly colorless oil. Anhydrous ether (300 ml.) was added causing almost immediate precipitation of the phosphonium bromide. The crude phosphonium salt was recrystallized twice from methylene chloride–ether to give 160 g. (87%) of the phosphonium bromide, m.p. 99–100°.

Anal. Calcd. for $C_{16}H_{34}BrO_2P$: C, 52.00; H, 9.28; Br, 21.63; P, 8.39. Found: C, 52.01; H, 9.35; Br, 22.00; P, 8.40.

cis-**Ethyl phenylglycidate** was synthesized according to the procedure of Speziale and Tung.[28] *threo*-Ethyl 3-chloro-2-hydroxy-3-phenylpropionate (20 g., 0.088 mole) was suspended in 560 g. of 7% aqueous sodium carbonate and heated at 50–55° for 2 hr. The mixture was cooled, extracted with methylene chloride, and the methylene chloride solution dried over anhydrous magnesium sulfate. The solvent was removed *in vacuo* and the resulting yellow oil distilled to yield 6.0 g. (36%) of *cis*-ethyl phenylglycidate, b.p. 78–80° (0.35 mm.), $n^{25}D$ 1.5096.

Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.73; H, 6.30. Found: C, 68.74; H, 6.32.

The n.m.r. spectra of the *cis*-epoxide was consistent with the proposed structure. The β-proton (doublet with a coupling

(25) M. L. Bender, R. D. Ginger, and J. P. Unik, *J. Am. Chem. Soc.*, **80**, 1044 (1958).
(26) All melting points are uncorrected. Analyses performed by Galbraith Laboratories, Inc., Knoxville, Tenn.
(27) O. Isler, H. Gutman, M. Montavan, R. Puezy, G. Reysen, and P. Zeller, *Helv. Chim. Acta*, **40**, 1242 (1957).
(28) A. J. Speziale and C. C. Tung, unpublished results.

constant of 5.0 c.p.s.) was observed at 5.84 τ and the α-proton (doublet with a coupling constant of 5.0 c.p.s.) at 6.27 τ. The corresponding protons in the *trans*-epoxide have coupling constants of 1.8 c.p.s.[28]

Kinetic Measurements.—Reagent grade solvents (benzene, chloroform, and methanol) were purified by the methods of Vogel[29] and stored over Fisher 4A molecular sieve. Benzene was stored over sodium.[30]

The rates of reaction of the ylids with aldehydes were determined by two methods, each of which gave the same results. In one case, aliquots from the reaction mixture were quenched in cold methanol (0°) and the ylid immediately titrated potentiometrically with aqueous HCl. The other method consisted of quenching aliquots from the reaction mixture in excess acid and back titration of the excess acid with aqueous sodium hydroxide. Both methods were thoroughly standardized with solutions containing known amounts of ylid and reaction products.

In a typical experiment, a solution of the ylid in the appropriate solvent was equilibrated at the desired temperature for at least 2 hr., and a known amount of aldehyde added at time zero. Aliquots of the reaction mixture were periodically withdrawn and treated as described above. Rate constants were calculated from the slopes of $1/C$ or log (A_0B/B_0A) vs. time plots. The kinetics of the reaction of carbethoxymethylenetributylphosphorane with p-methoxybenzaldehyde were performed in a nitrogen atmosphere.

The rate of olefin formation in the reaction of carbomethoxymethylenetriphenylphosphorane with p-methoxybenzaldehyde in benzene was determined as follows: Aliquots of the reaction mixture were removed and extracted twice with a volume of aqueous hydrochloric acid sufficient to remove all of the ylid. (Both the ylid and phosphonium salt react quantitatively with bromine.) The organic phase was then added to a volume of standard $Br_3^\ominus$ in methanol[31] containing 1.5–2.0 times as much Br_2 as would be required by the olefin. The mixture was allowed to stand in the dark for 1 hr. (a longer period did not affect results) and the excess bromine titrated with a standard solution of anethole in methanol.[32]

Competition Experiments.—The competition experiments were performed in two ways. In one case a solution of the ylid in

(29) A. J. Vogel, "Practical Organic Chemistry," Longmans, Green and Co., New York, N. Y., 1956.

(30) It was found that the values of rate constants obtained in benzene depended upon the method of purification of the benzene. When the benzene was washed with concentrated sulfuric acid prior to distillation from sodium, the rate constants were consistently slightly higher than when the A.R. grade benzene was simply distilled from sodium.

(31) J. Mitchell, I. R. Kolthoff, E. S. Proskauer, and A. Weissberger, "Organic Analysis," Vol. III, Interscience Publishers, Inc., New York, N. Y., p. 239.

(32) L. N. Petrova, Zh. Priklad. Khim., 22, 122 (1949).

chloroform was added slowly to a solution of a threefold excess of both benzaldehyde and p-nitrobenzaldehyde (m-chlorobenzaldehyde). In each case the product isolated was exclusively that arising from reaction of the ylid with the substituted aldehyde. Product ratios were determined by gas chromatographic analysis of the chloroform solution and by isolation of the products. In the second case, a mixture of benzaldehyde and m-chlorobenzaldehyde in various proportions was added rapidly to a solution of the ylid. In this competition experiment, some reaction of the ylid with benzaldehyde was always observed; however, the major product was still that arising from the more reactive aldehyde (Table V). In a typical experiment, 1.0 g. (0.00287 mole) of carbethoxymethylenetriphenylphosphorane was dissolved in 15 ml. of absolute ethanol, heated to reflux, and treated with an ethanolic solution of 0.305 g. (0.00287 mole) of benzaldehyde and 0.405 g. (0.00287 mole) of m-chlorobenzaldehyde. The solution was refluxed under nitrogen 16 hr., cooled, and the solvent removed *in vacuo* in the cold. The residue was then dissolved in 3 ml. of methylene chloride and the resulting solution analyzed with v.p.c.

Epoxide Ring Opening Reactions.—All of these experiments were performed in refluxing anhydrous ethanol. In a typical experiment, the epoxide (0.008 mole) and the appropriate amount of m-chlorobenzaldehyde (0.024 mole) were dissolved in 15 ml. of ethanol, and the solution was heated to reflux and a solution of the phosphine (0.008 mole) in 15 ml. of ethanol added. The solution was refluxed for a specified length of time. Nitrogen was passed through the solution throughout the period of reflux. When tributylphosphine was used, a reflux time of 20 hr. was utilized for the *trans*-epoxide and 42 hr. for the *cis*-epoxide. For triphenylphosphine it was necessary to reflux the *trans*-epoxide reaction 5 days and the *cis*-epoxide reaction 10 days. The extent of reaction was determined by periodically removing aliquots of the solution and adding these to an ethanolic solution of mercuric chloride.[33] When an aliquot showed the absence of unreacted phosphine, the solutions were cooled and analyzed with v.p.c.[34] Retention times for all of the products were compared with those of authentic samples. The products from one reaction were isolated with preparative v.p.c. and the aldehydes identified by oxidation to the corresponding acids and comparison *via* melting point and mixture melting point with authentic samples. The unsaturated esters were identified by comparison of their infrared spectra with those of authentic samples.

(33) Triphenylphosphine and tributylphosphine form ethanol-insoluble complexes with mercuric chloride.

(34) A 5-ft. column of 20% Apiezon L on Chromosorb W maintained at 180° was used in all gas chromatographic analyses.

COMMUNICATIONS TO THE EDITOR

Aroylation at the Terminal Methyl Group of a 1,3,5-Triketone to Form a 1,3,5,7-Tetraketone[1]

Sir:

Although acetylacetone can be benzoylated at one of its terminal methyl groups with methyl benzoate by means of two equivalents of potassium amide in liquid ammonia to form I,[2] attempts in this Laboratory to further benzoylate I at its remaining methyl group by means of three molecular equivalents of this reagent to give II have been unsuccessful.

$C_6H_5COCH_2COCH_2COCH_3$ $C_6H_5COCH_2COCH_2COCH_2COC_6H_5$
          I   II
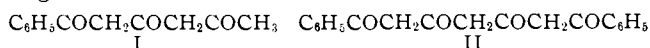
We now wish to report that not only the terminal benzoylation of acetylacetone[3] but also the terminal benzoylation of I to form II can be accomplished by means of sodium hydride in 1,2-dimethoxyethane.
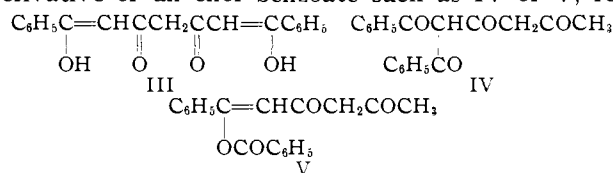
(1) This research was supported by grants from the National Science Foundation and the National Institutes of Health.

(2) C. R. Hauser and T. M. Harris, J. Am. Chem. Soc., 80, 6360 (1958); R. J. Light and C. R. Hauser, J. Org. Chem., 25, 538 (1960).

(3) Aroylations of benzoylacetone with methyl benzoate and methyl anisate to form the corresponding 1,3,5-triketones have been effected with sodium hydride in yields of 87–92% (based on the β-diketone), which are twice those obtained previously by means of potassium amide in liquid ammonia (see ref. 2). The details will be published soon.

Thus, II, m.p. 91–93°, was obtained in 52% yield. *Anal.* Calcd. for $C_{19}H_{16}O_4$: C, 74.02; H, 5.22. Found: C, 73.83; H, 5.06. This appears to be the first example of an acyclic 1,3,5,7-tetraketone that has been isolated and characterized.

That the product was the terminal methyl derivative II (in an enol form such as III), not a methylene derivative or an enol benzoate such as IV or V, respectively,

$C_6H_5C{=}CHCCH_2CCH{=}CC_6H_5$ $C_6H_5COCHCOCH_2COCH_3$
    | ‖   ‖ | |
   OH   O   O   OH C_6H_5CO
          III   IV
       $C_6H_5C{=}CHCOCH_2COCH_3$
               |
            $OCOC_6H_5$
               V

spectively, was supported by its n.m.r. spectrum (in deuterated chloroform using tetramethylsilane as an internal standard), which showed peaks corresponding to the protons of the units $COCH_2$ (3.55 p.p.m.) and $C{=}CH$ (6.32 p.p.m.), but no peak indicative of a terminal methyl group as would be shown by IV or V.[4] An n.m.r. spectrum of the parent compound

(4) If the spectrum is obtained immediately after dissolving the tetraketone in deuterated chloroform, it shows a series of peaks corresponding to several enolic forms of II. After several hours at room temperature, this