solution of ethyl acetate of known concentration. Analysis by glc (5 ft × 1/8 in. 3% SE-30 on Variport column, 80°, flow 25 ml/min of nitrogen), relative to a biphenyl internal standard and a standard mixture of acetophenone and biphenyl in carbon tetrachloride solution, indicated a quantitative yield of acetophenone.

Kinetic Methods. Iodometrically determined rates were made by a standard procedure.[9] For nmr data, the reactions were carried out in sealed nmr tubes. The tubes were periodically withdrawn from a constant temperature oil bath and quenched in a −78° bath. After warming to room temperature, the nmr spectrum was immediately measured and the 1,2-dioxetane methyl and methylene as well as reference absorptions were integrated. The rate of decomposition of the 1,2-dioxetanes was slow enough at room temperature that essentially no decomposition occurred during the measurements. For **1**, benzene was added to the solution as an internal reference and the total aromatic absorption was used as the reference for **2**. Area ratios of the methyl 1,2-dioxetane to reference absorptions were normally used to calculate the rate coefficients with the aid of a standard least-squares first-order computer program. The methylene absorptions of the 1,2-dioxetanes gave essentially the same rate coefficients, but usually with less precision.

Acknowledgment. This investigation was supported by the Petroleum Research Fund, administered by the American Chemical Society, and by the U. S. Army Research Office (Durham). We wish to acknowledge the helpful assistance of Dr. Vernon F. Hodge in the early stages of this work.

On the Kinetics and Mechanism of the Perkow Reaction[1]

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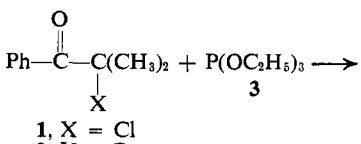
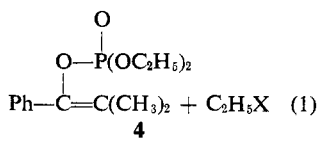
Abstract: The reactions of aryl-substituted α-chloroisobutyrophenones and α-bromoisobutyrophenones with triethyl phosphite to give diethyl 1-phenyl-2,2-dimethylvinyl phosphate (the Perkow reaction) have been studied kinetically by an nmr technique. The reactions are second order overall and they exhibit a moderate solvent effect. The chloro ketones react 1.1–2.7 times faster than the corresponding α-bromo ketones. ρ values for the two series are 1.89 and 2.37, respectively. The reaction of α-chloroisobutyrophenone with triethyl phosphite exhibits a marked catalysis by added acetic acid which is proportional to the concentration of acid. This and other accumulated data support a mechanism for the Perkow reaction involving a rate-determining addition of phosphite to carbonyl carbon followed by rearrangement of the phosphorus to oxygen. The stereochemistry of the carbonyl addition is proposed as occurring mainly from the less hindered side of the halogen eclipsed or gauche forms of the α-halo ketone. This is a rationalization of our recent findings that the vinyl phosphate *E* isomer is more predominantly formed from bromo ketones than from chloro ketones.

The Perkow reaction is exemplified by the reaction of α-chloroisobutyrophenone (**1**) or α-bromoisobutyrophenone (**2**) with triethyl phosphite (TEP, **3**) to give diethyl 1-phenyl-2,2-dimethylvinyl phosphate (**4**, eq 1).[3]



1, X = Cl
2, X = Br



(1)

Although numerous studies have appeared on the scope and mechanism of the Perkow reaction,[3,4] no kinetic studies have been reported. We wish to report a kinetic study on the reactions of a series of aryl-substituted α-chloroisobutyrophenones and α-bromoisobutyrophenones with triethyl phosphite wherein rates, activation parameters, Hammett ρ values, and the effect upon rates of solvent and added acetic acid have been determined. Some new nonkinetic data will also be presented. A suggested mechanism based on the accumulated data will be presented and discussed. Our recent finding that the *E* isomeric vinyl phosphate usually predominates will be rationalized.

Results

The reaction of **1** or **2** with **3** was studied in benzene using an nmr technique (see Experimental Section). The reactions are first order in halo ketone and first order in **3**, as shown by linear plots of $x/(a - x)$ *vs.* time. The relative constancy of k_{obsd} for the reaction of **2** with **3** for differing ratios of reactants is shown in Table I.

The reactions give the vinyl phosphate **4** as the only product. The rates and relative rates of reaction of aryl-substituted **2** with **3** at 44.9° are given in Table II.

(1) This investigation was supported by Grant No. AF-AFOSR 1170-66, 1170-67 from the Directorate of Chemical Sciences, Air Force Office of Scientific Research, and by the National Science Foundation at Yeshiva University. This is part XVII of the series, Organophosphorus Chemistry.

(2) To whom correspondence should be addressed at Yeshiva University.

(3) I. J. Borowitz, M. Anschel, and S. Firstenberg, *J. Org. Chem.*, **32**, 1723 (1967).

(4) (a) F. W. Lichtenthaler, *Chem. Rev.*, **61**, 607 (1961); (b) P. A. Chopard, V. M. Clark, R. F. Hudson, and A. J. Kirby, *Tetrahedron*, **21**, 1961 (1965). (c) NOTE ADDED IN PROOF. See A. Arcoria and S. Fisichella, *Tetrahedron Lett.*, 3347 (1971), for kinetics of diethyl 1-phenylvinyl phosphate formation.

Table I. Reaction of α-Bromoisobutyrophenone with TEP at 44.9 ± 0.03°

[Bromo ketone 2],[a] *M*	[TEP, 3], *M*	[2]/[3]	10^5k_2, M^{-1} sec^{-1}
0.8881	0.8881	1.0	1.16 ± 0.005
0.9055	0.4509	2.0	1.01 ± 0.03
0.4703	0.9406	0.5	0.986

[a] All reactions in dry benzene.

Table II. Reactions of Aryl-Substituted α-Bromoisobutyrophenones with TEP in Benzene at 44.9 ± 0.03°

Aryl substituent		10^5k_2, M^{-1} sec^{-1}	k/k_0
None	**2**	1.16 ± 0.005	1.00
p-CH_3	**2a**	0.458 ± 0.005	0.39
p-OCH_3	**2b**	0.234 ± 0.005	0.20
m-OCH_3	**2c**	0.819 ± 0.04	0.70
p-Cl	**2d**	2.47 ± 0.07	2.12
m-Cl	**2e**	3.72 ± 0.24	3.19
m-NO_2	**2f**	20.17 ± 0.91	17.4

Table III. Solvent Effect upon Rate of Reaction of **2** with TEP

Solvent	Temp, °C	10^5k_2, M^{-1} sec^{-1}
C_6H_6	30.0 ± 0.03	0.329 ± 0.004
	44.9	1.16 ± 0.005
	65.3	3.36 ± 0.11
C_6H_5CN	22.2	0.388 ± 0.002
	44.9	2.70 ± 0.06

The rates and relative rates of the reactions of aryl-substituted α-chloroisobutyrophenones with **3** are given in Table V. The rates are all faster than for the corresponding α-bromo ketone. A linear Hammett ρ plot with ρ = 2.37 (confidence level 99.9%) is obtained.[5]

Activation parameter data for the reactions of **2** with TEP in benzene and in benzonitrile and for **1** with TEP in benzene are given in Table VI. The data are based on rate data in Table III for **2** and **1** at 44.9° (Table V) and at 62.0° (k_2 = 4.47 ± 0.06 × 10^{-5} M^{-1} sec^{-1}).

Effect of Added Acid. The reaction of **2** with TEP (**3**) increases in rate approximately in proportion to the concentration of added acetic acid (Table VII) in the range of 0.0023–0.028 *M*. The rate increase is much greater than can be attributed to a polar solvent effect. There is a negative departure from linearity at the higher acid concentrations which may be due to protonation of phosphite or some other interaction which lowers the effective phosphite concentration.

Discussion

Among the mechanisms proposed for the Perkow reaction, the more likely ones include (1) the addition of phosphite to carbonyl carbon followed by a rearrangement of the phosphorus moiety (in **6**) to oxygen to give an enol phosphonium halide **8**, (2) a concerted addition of phosphite to carbonyl oxygen to give **8** directly, (3) a nonconcerted addition of phosphite to carbonyl oxygen to give a carbanion oxyphosphonium dipole **10**[6] which then is converted to **8**, and (4) an addition of phosphite across the carbonyl to give a pentacovalent species **7**. The latter is a tautomer of **6** and **10**. Both **6** and **7** should readily convert to **8** which should then rapidly be converted to the vinyl phosphate **9**. The last step, an Arbuzov cleavage of an alkoxyl group by halide ion, has been shown to be rapid and not rate determining in the reaction of TEP with ethyl iodide.[7] We have assumed that it cannot be the rate-determining step in our reactions and the data bear this out.

Table IV. Comparison of Rates of Reaction for Triethyl and Triisopropyl Phosphite with α-Bromoisobutyrophenones in Benzene at 44.9°

Aryl substituent		$(RO)_3P$	10^5k_2, M^{-1} sec^{-1}	k/k_0	k_2(Et)/k_2(*i*-Pr)
None	**2**	ethyl	1.16 ± 0.005	1.00	2.73
m-Cl	**2e**	ethyl	3.72 ± 0.24	3.19	2.31
m-OCH_3	**2c**	ethyl	0.819 ± 0.04	0.70	2.24
None	**2**	isopropyl	0.425 ± 0.006	1.00	
m-Cl	**2e**	isopropyl	1.61 ± 0.0	3.79	
m-OCH_3	**2c**	isopropyl	0.365 ± 0.004	0.86	

Table V. Reactions of Aryl-Substituted α-Chloroisobutyrophenones with TEP in Benzene at 44.9 ± 0.03°

Aryl substituent		10^5k_2, M^{-1} sec^{-1}	k/k_0	k_2(Cl)/k_2(Br)
None	**1**	1.59 ± 0.01	1.00	1.37
p-OCH_3	**1b**	0.262 ± 0.001	0.16	1.11
p-Cl	**1d**	4.20 ± 0.02	2.64	1.70
m-OCH_3	**1c**	2.20 ± 0.07	1.38	2.68
m-Cl	**1e**	9.33 ± 0.17	5.84	2.51

The data give a linear Hammett ρ plot with ρ = 1.89 (confidence level 99.9%) using σ values and poorer correlations using mixtures of σ and σ⁻.[5]

The reaction of **2** with **3** is faster in the more polar solvent benzonitrile (dielectric constant = 25.6) than in benzene (dielectric constant = 2.3) by a ratio of 2.32 at 44.9° (Table III).

The effect of changing the alkyl group of the trialkyl phosphite in reaction with **2**, **2c**, and **2e** (*m*-Cl) was briefly studied (Table IV). Triethyl phosphite (**3**) was found to react faster than does triisopropyl phosphite (**5**) with **2**, **2c**, or **2e**. The rate of reaction of **2** with trimethyl phosphite could not be accurately determined due to a side reaction of methyl bromide with trimethyl phosphite. The similar rate ratios of *m*-Cl/H and *m*-OCH_3/H in reaction with **3** or **5** suggest that the ρ value for the reactions of aryl-substituted **2** with **5** will be similar to that with **3**.

(5) Computed by Professor M. Charton, Pratt Institute.

(6) Such species are probably involved in the reactions of phosphites with (a) fluorenones: I. J. Borowitz, M. Anschel, and P. D. Readio, *J. Org. Chem.*, **36**, 553 (1971); I. J. Borowitz and M. Anschel, *Tetrahedron Lett.*, 1517, 5032 (1967); F. Ramirez and C. P. Smith, *Chem. Commun.*, 662 (1967); (b) dibenzoylethylene: F. Ramirez, O. P. Madan, and C. P. Smith, *Tetrahedron*, **22**, 567 (1966); and (c) hexafluoroacetone: F. Ramirez, A. S. Gulati, and C. P. Smith, *J. Amer. Chem. Soc.*, **89**, 6283 (1967).

(7) G. Aksnes and D. Aksnes, *Acta Chem. Scand.*, **18**, 38 (1964).

Table VI. Activation Parameters for α-Haloisobutyrophenone–Triethyl Phosphite Reactions

Halo ketone	Solvent	E_a, kcal/mol	$\Delta S^{\ddagger}$, eu[d]	$\Delta H^{\ddagger}$, kcal/mol[d]	$\Delta G^{\ddagger}$, kcal/mol[e]
α-Bromoisobutyrophenone	benzene	13.3[a]	−41	12.7	25.8
	benzonitrile	16.0[b]	−31	15.3	25.3
α-Chloroisobutyrophenone	benzene	12.8[c]	−42	12.2	25.6

[a] From data at 30, 44.9 and 65.3°. [b] From data at 22.2 and 44.9°. [c] From data at 44.9 and 62.0°. [d] At 44.9°. [e] At 44.9° from $\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$.

Table VII. Effect of Acetic Acid on the Reaction of α-Chloroisobutyrophenone with TEP at 62.1° in Benzene. $[TEP]_0 = [1]_0 = 0.500\ M$

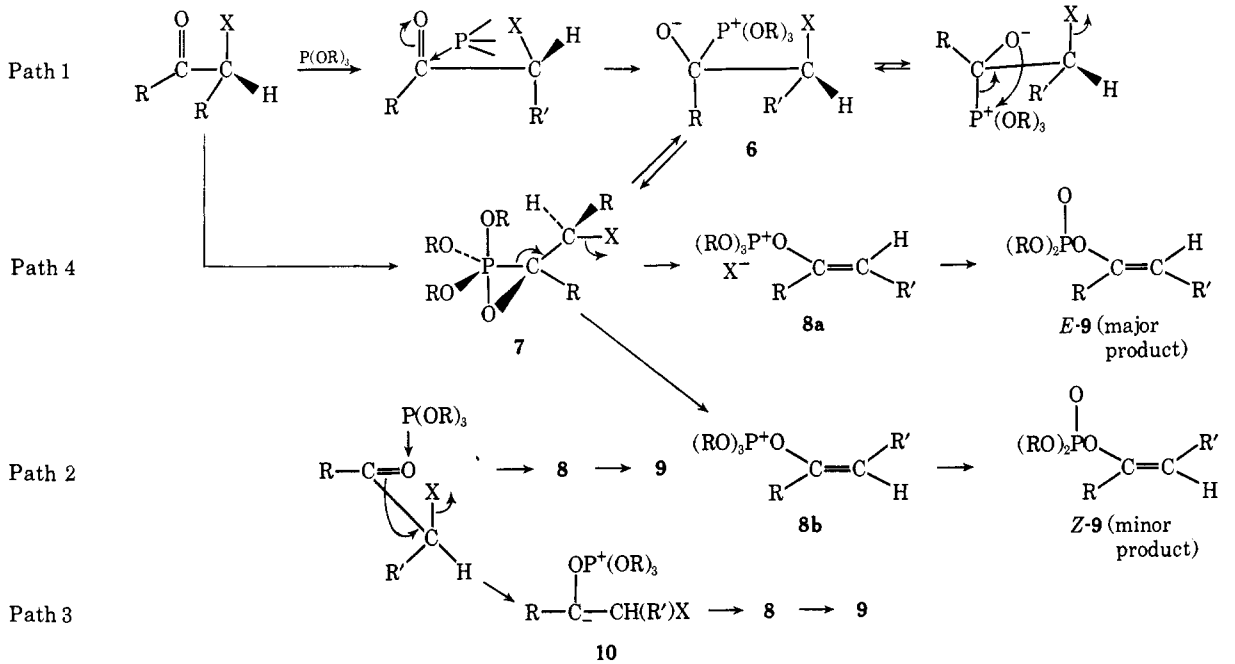
[Acetic acid], M	$10^5 k_2$,[a] M^{-1} sec^{-1}
0.00	5.68
0.00233	6.70
0.00546	7.41
0.01093	8.30
0.0278	10.94

[a] All rate constants are ±~0.2.

Pathway 2, formally an SN2′ type of reaction, involves the loss of halide ion in a rate-determining step. This pathway is not compatible with the fact that the chloroisobutyrophenones react faster than do the bromoisobutyrophenones. Furthermore, $k_2(Cl)/k_2(Br)$ = 1.6 for the reactions of *p*-nitro-α-bromoacetophenone (**11**) or *p*-nitro-α-chloroacetophenone (**12**) with **3**,[8] and *ca.* 1.0 for α-bromocyclohexanone (**13**) or α-chlorocyclohexanone (**14**) with **3**.[3] The role of acid catalysis is not clear *via* pathway 2. Protonation of halogen could be involved but it is not very likely.[9] The predominant formation of the *E* isomer **9** (Scheme I) is also hard to rationalize by this pathway. A rate-determining addition of phosphite across the carbonyl with more bond formation at oxygen than at carbon should result in a correlation with a mixture of σ and σ⁻.[10] A full addition of phosphite to carbonyl oxygen in the rate-determining step should result in a carbanion oxyphosphonium dipolar species **10** (pathway 3) which should correlate with σ⁻. The stabilization of such a species, especially for halo ketones such as **13** or **14** which contain no phenyl groups, is questionable. Previous work suggests that species such as **10** are obtained only when the negative charge is stabilized by strongly electron-withdrawing groups (*p*-NO_2, CF_3), or by being part of a cyclopentadienyl anion system.[6,11,12]

We have previously rejected a mechanism for the Perkow reaction involving initial attack by phosphite on the halogen of an α-halo ketone to give an ion pair which then recombines to give the enol phosphonium halide **8**. Among other evidence against this pathway (also rejected by Hudson[4b]) are our observations that acetic acid enhances the formation of vinyl phosphates from α-bromo ketones at the expense of ketophosphonates,[3] the presently indicated acid catalysis for the reaction of **1** with TEP, and the absence of dehalogenation in the presence of protic species. These observations are in marked contrast to the behavior of triphenylphosphine (TPP) with hindered α-bromo ketones wherein we have shown that enol phosphonium salts

Scheme I



(8) R. K. Crouch, unpublished observations.
(9) The general role of protonated α-halo ketones has been questioned: G. C. Levy, J. D. Cargioli, and W. Racela, *J. Amer. Chem. Soc.*, **92**, 6238 (1970).
(10) J. E. Leffler and E. G. Grunwald, "Rates and Equilibria of Organic Reactions," Wiley, New York, N. Y., 1963: (a) p 211; (b) pp 178–182.
(11) F. Ramirez, *Accounts Chem. Res.*, **1**, 168 (1968).
(12) M. J. Gallagher and I. D. Jenkins, *J. Chem. Soc. C*, 2605 (1971).

are formed *via* attack on halogen.[13] Furthermore, traces of acid catalyze the debromination of all α-bromo ketones with TPP in protic solvents.[14] This includes cases wherein either keto or enol phosphonium salts are formed in anhydrous solvents.

This leaves pathways 1 and 4. We believe that the available data are best explained by pathway 1 involving a rate-determining addition of phosphite to carbonyl carbon, possibly of the eclipsed rotamer of the halo ketone, followed by faster rearrangement and Arbuzov cleavage steps. The large negative entropies of activation obtained, even in the polar solvent benzonitrile, are consistent with an ordered and probably a dipolar transition state. The ρ data and solvent effect noted are also consistent with such a transition state.

Rate-determining carbonyl addition could explain why α-chloro ketones react more rapidly with TEP than do the corresponding bromo ketones. The larger inductive effect and smaller steric effect of chlorine, as compared with bromine, may both contribute to the observed $k_2(\mathrm{Cl})/k_2(\mathrm{Br})$ ratio. Ratios of $k_2(\mathrm{Br})/k_2(\mathrm{Cl}) \cong 23$–50 are ordinarily found for SN2 displacements.[15] The reaction of α-bromoacetophenone with TPP has a $k_2(\mathrm{Br})/k_2(\mathrm{Cl})$ ratio of 162.[16] The observation of a small $k_2(\mathrm{Cl})/k_2(\mathrm{Br})$ ratio is taken as strong evidence against halide ion loss occurring in the rate-determining step of the Perkow reaction. An evaluation of what the magnitude of $k_2(\mathrm{Cl})/k_2(\mathrm{Br})$ should be for rate-determining addition to carbonyl of halo ketones is not available on the basis of known data. Steric effects are apparently quite prominent in the Perkow reaction, as evidenced by the slower reaction of **2** or **2e** with triisopropyl phosphite than with TEP. Whether this provides evidence for the involvement of pentacovalent forms such as **7** is not clear. One can argue for the participation of such species based on data obtained in the Wittig reaction (see below).

The reaction of benzil with trialkyl phosphites has been postulated to proceed *via* a similar mechanism.[17] Acid catalysis and solvent effects qualitatively similar to those noted in our reactions were observed. Inspection of Ogata's data shows a rate attenuation by stronger acids presumably related to our observations. A steric effect for bulky phosphites was observed in that the rate increased in the order CH_3 < *sec*-butyl < ethyl < isopropyl; *i.e.*, the rate constant for *sec*-butyl was smaller than expected on electronic grounds. An entropy of activation in dioxane, −47.5 eu, similar to ours, was obtained. The reactions are about 100 times faster than those of **1** with TEP in solvents of reasonably similar polarity. This could be due to the greater activation to carbonyl addition of an adjacent carbonyl rather than adjacent carbon–halogen. Lesser steric effects are present in the benzil system perhaps because the conformation of the α-diketone is s-trans while the halo ketones **1** and **2** react in their eclipsed forms (or related gauche forms).

The Wittig reaction of carbomethoxymethylene triphenylphosphorane with substituted benzaldehydes, in which the rate-determining step is a reversible carbonyl addition, has E_a = 10.7 kcal/mol, $\Delta S^{\ddagger}$ = −41.6 eu, and ρ = +2.7 (in benzene), data quite similar to ours.[18] The addition of nitrogen nucleophiles to carbonyls exhibits similar ρ values. Thus the reaction of aryl-substituted benzaldehydes with semicarbazide has an equilibrium ρ = 1.81[19a] and the saponification of benzoate esters has ρ = 1.9–2.4.[10b]

Whether or not the phosphite addition is reversible is not known. One can argue that many carbonyl additions are reversible.[19b] However, the rearrangement of **6** or **7** (Scheme I) should be facile so that k_2 might be larger than k_{-1} making the latter insignificant. The point is important when we seek to rationalize our finding that the (*E*)-vinyl phosphate is the sole or predominant product from several α-bromo ketones and the major product (1.6–3.0:1) from the corresponding chloro ketones.[20] If the addition of phosphite to carbonyl is irreversible and subject to kinetic control, the application of Cram's rule[21] to the gauche halo ketone rotamer can explain the predominant formation of the (*E*)-vinyl phosphate, such as **9** (eq 2, R = R′ = Ph), from α-bromobenzyl phenyl ketone (**15**) while the less bulky α-chlorobenzyl phenyl ketone (**16**) gives a 2:1 product ratio of the *E* and *Z* isomers.[20] The assumption that α-halo ketones react with phosphites, and possibly with other nucleophiles, *via* their eclipsed forms, gains some credence from studies by Karabatsos and others which indicate that the eclipsed form is favored in solution in the ground state for α-chloroacetaldehyde,[22a] α,α-dichloroacetaldehyde,[22b] and some α-chloro ketones.[23] Furthermore recent calculations by Allen[24] indicate that the eclipsed form is more stable in the ground state for a number of carbonyl compounds. The related gauche forms of α-halo ketones could be readily obtained in phosphite reactions because of phosphite halogen repulsion in the transition state for carbonyl addition. Whether there is any correlation between the preferred rotamer distribution in the ground state (wherein measured energy differences are *ca.* 1.5 kcal/mol)[22a] and in the transition state leading to the Perkow reaction (E_a = 13–15 kcal/mol) is, of course, questionable.[21b]

(13) I. J. Borowitz, K. C. Kirby, P. E. Rusek, and E. W. R. Casper, *J. Org. Chem.*, **36**, 88 (1971).

(14) (a) H. Parnes and E. Lord, unpublished observations; (b) H. Parnes, Ph.D. Thesis, Yeshiva University, 1970.

(15) (a) A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill, New York, N. Y., 1962, pp 7–30, 82; (b) E. Kosower, "An Introduction to Physical Organic Chemistry," Wiley, New York, N. Y., 1968, pp 63–82; (c) D. J. Pasto, K. Garves, and M. P. Serve, *J. Org. Chem.*, **32**, 774 (1967); (d) T. I. Temnikova and V. S. Karavan, *J. Gen. Chem. USSR*, **34**, 3204 (1964).

(16) (a) I. J. Borowitz and H. Parnes, *J. Org. Chem.*, **32**, 3560 (1967). (b) Phosphorus nucleophiles may generally show a large $k_2(\mathrm{Br})/k_2(\mathrm{Cl})$ ratio. Thus di-*n*-butyl phosphite or tributylphosphine react faster with propyl bromide than with propyl chloride by 246:1 and 125:1 ratios, respectively; see R. F. Hudson, "Structure and Mechanism in Organophosphorus Chemistry," Academic Press, New York, N. Y., 1965, p 124.

(17) Y. Ogata and M. Yamashita, *J. Amer. Chem. Soc.*, **92**, 4670 (1970).

(18) A. J. Speziale and D. E. Bissing, *ibid.*, **85**, 3878 (1963).

(19) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969: (a) pp 480–497; (b) pp 463–554.

(20) I. J. Borowitz, S. Firstenberg, E. W. R. Casper, and R. K. Crouch, *J. Org. Chem.*, **36**, 3282 (1971).

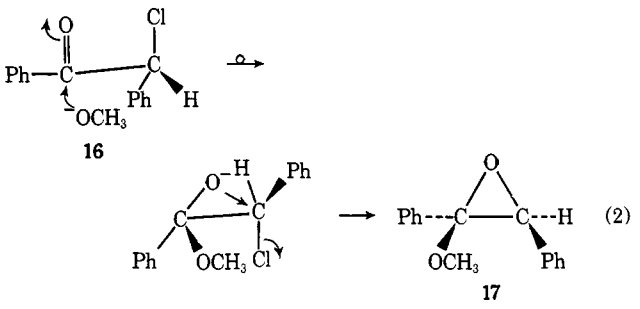
(21) (a) D. J. Cram and F. A. Abd Elhafez, *J. Amer. Chem. Soc.*, **74**, 5828 (1952); (b) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965, pp 32–35; (c) O. H. Wheeler in "Chemistry of the Carbonyl Group," S. Patai, Ed., Interscience, New York, N. Y., 1966, pp 550–553.

(22) (a) G. J. Karabatsos and D. J. Fenoglio, *J. Amer. Chem. Soc.*, **91**, 1124 (1969); (b) G. J. Karabatsos, D. J. Fenoglio, and S. S. Lande, *ibid.*, **91**, 3572 (1969).

(23) S. Z. Mizushima, T. Shimanouchi, T. Miyazawa, I. Ichishima, K. Kuratani, I. Nakagawa, and N. Shido, *J. Chem. Phys.*, **21**, 815 (1953).

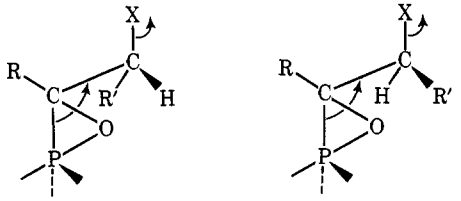
(24) R. B. Davidson and L. C. Allen *ibid.*, **54**, 2828 (1971).

The application of Cram's rule to eclipsed or gauche halo ketone rotamers can also explain the reaction of α-chlorobenzyl phenyl ketone (**16**) with methoxide to give the *trans*-diphenylmethoxy epoxide **17**.[25] Unfortunately **17** is probably an equilibratible system, and it is suspected that the corresponding *cis*-diphenyl isomer **18**, if formed initially, might readily convert to **17** which should be more stable. Known irreversible addition reactions of α-halo ketones with nucleophiles, in which such ambiguity does not exist and in which Cram's rule should apply, usually involve Grignard reactions.[26] In these cases formation of the major isomeric product has been rationalized by the addition of the nucleophile to the less hindered side of the carbonyl in the staggered halo ketone rotamer.[27] It may be, however, that in these reactions the halo ketone carbonyl is coordinated with a Lewis acid, such as magnesium halide, thus negating the attractive forces which stabilize the eclipsed halo ketone rotamer. Such coordinated species would be expected to be more stable in the staggered conformation for steric reasons.[21]



16 **17** (2)

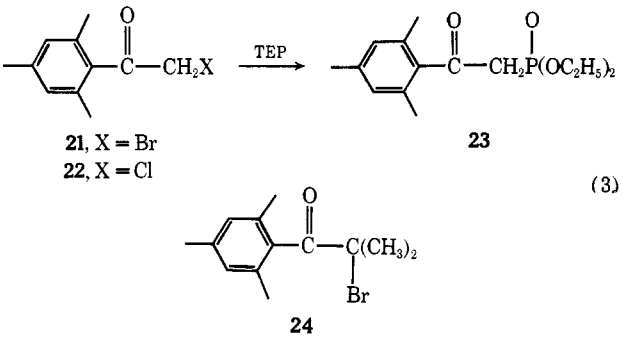
The assumption of thermodynamic control for the formation of vinyl phosphates from a carbonyl adduct *via* an anti elimination suggests that the form **20**, leading to the *Z* isomeric vinyl phosphate, should be energetically more favorable than is **19**.[28] Clearly, more research is needed on the stereochemistry of addition of nucleophiles to α-halo ketones *via* kinetic and thermodynamic control.



19 **20**

Supporting Data[29]

The α-bromo and α-chloro ketones **21** and **22** react with TEP to give the ketophosphonate **23** as the only product. The α-bromo ketone **21** reacts much more rapidly than does **22** (see Experimental Section). This set of halo ketones constitutes one of the few pairs of bromo and chloro ketones which react with TEP to give ketophosphonate products and in which $k_2(Br)/k_2(Cl)$ is large.[30] Vinyl phosphate formation is presumably excluded because of the hindrance of the carbonyl carbon to addition. Trimethylphenyl-α-bromoisobutyrophenone (**24**) gives no reaction with TEP since both SN2 substitution and carbonyl addition reactions are now sterically retarded.



21, X = Br
22, X = Cl
23 (3)

24

We conclude that hard and soft acid–base theory[31] can be applied to the reactions of tricovalent organophosphorus species with α-halo ketones and other carbonyl compounds and that triphenylphosphine is "softer" than are trialkyl phosphites. Thus triphenylphosphine reacts at the "softer" sites of an α-halo ketone halogen or carbon of the carbon–halogen bond,[13] while the relatively "harder" phosphites react at the "harder" carbonyl sites.

Experimental Section[32]

The unsubstituted α-haloisobutyrophenones,[3] α-halo-2,4,6-trimethylacetophenones,[30] other halo ketones,[3,4b] and trialkyl phosphites have been previously described. Aryl-substituted isobutyrophenones were prepared by (1) procedure A, the reaction of a substituted benzaldehyde with isopropylmagnesium halide followed by chromic acid oxidation, and (2) procedure B, the Friedel–Crafts alkylation of a substituted benzene with isobutyryl chloride. They were characterized by their nmr spectra which confirmed meta or para substitution. Procedure B gave isolable ortho substituted, as well as para substituted, product only from toluene. *p*-Methylisobutyrophenone, 65% *via* procedure A, had bp 64–65° (0.20 mm) [lit.[33] bp 102–103° (6 mm)]; nmr (neat) τ 2.1–2.9 (m, 4, aryl), 6.6 (q, 1, CH), 7.65 (s, 3, aryl CH_3), 8.9 (d, 6, CH_3).

m-Methoxyisobutyrophenone, 73% *via* procedure A, had bp 75–80° (0.20 mm) [lit.[34] bp 130° (12 mm)]; nmr (CCl_4) τ 2.6 (m, 4, aryl), 6.3 (s, 3, OCH_3), 6.6 (m, 1, CH), 8.9 (d, 6, CH_3).

p-Chloroisobutyrophenone, 37% *via* procedure A, had bp 130–131° (7 mm) [lit.[35] bp 100–104° (1 mm)]; nmr (neat) τ 2.5 (m, 4, aryl), 6.6 (septet, 1, CH), 8.9 (d, 6, CH_3).

m-Nitroisobutyrophenone, 66% by nitration of isobutyrophenone, had bp 128–130° (0.60 mm) [lit.[36] mp 37°]; nmr (neat) τ 1.15–2.3 (m, 4, aryl), 6.25 (septet, 1, CH), 8.7 (d, 6, CH_3).

m-Chloroisobutyrophenone, 41% *via* procedure A, had bp 66–67° (0.45 mm); nmr (CCl_4) τ 2.6 (m, 4, aryl), 6.55 (septet, 1, CH), 8.9 (d, 6, CH_3); mass spectrum (70 eV) *m/e* 182.0508 (M^+) (calcd for $C_{10}H_{11}OCl$, 182.0498).

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(29) The reaction of α-chlorothioacetone with phosphites occurs by addition to thiocarbonyl carbon: E. Gaydou, G. Peiffer, and A. Guillemonat, *Tetrahedron Lett.*, 239 (1971).
(30) Halo ketones **21** and **22** have previously been shown to give **23**: R. F. Hudson and G. Salvadori, *Helv. Chim. Acta*, **49**, 96 (1966). In contrast, **21** reacts with methylpropylphenylphosphine to give the enol phosphonium salt, probably *via* attack on bromine.[13]
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p-Methoxyisobutyrophenone, 59% *via* procedure A, had bp 110–111° (0.25 mm) [lit.[37] bp 82–87° (0.01 mm)]; nmr (CCl_4) τ 2.1–3.1 (m, 4, aryl), 6.2 (s, 3, OCH_3), 6.55 (septet, 1, CH), 8.9 (d, 6, CH_3).

2,4,6-Trimethylisobutyrophenone, 79% *via* procedure B, had bp 146–147° (11 mm) [lit.[38] bp 120–121° (10 mm)]; nmr (CCl_4) τ 3.2 (m, 2), 7.78 (s, 3), 7.80 (s, 6, OCH_3), 8.1 (d, 6, CCH_3).

The isobutyrophenones were converted to the α-chloro ketones with sulfuryl chloride and to the α-bromo ketones with bromine. The halo ketones were distilled to remove unreacted ketone. They all had nmr (CCl_4 or neat) peaks at *ca.* τ 2.0–2.9 (m, 4, aryl), 8.1 (s, 6, CH_3), and (for the methoxy compounds) 6.2 (s, 3, OCH_3).

α-Bromo-*m*-methoxyisobutyrophenone (**2c**), 49%: bp 96–97° (0.15 mm). *Anal.* Calcd for $C_{11}H_{13}O_2Br$: C, 51.37; H, 5.09. Found: C, 51.17; H, 4.98.

α-Chloro-*m*-methoxyisobutyrophenone (**1c**), 86%: bp 164–165° (28 mm). *Anal.* Calcd for $C_{11}H_{13}O_2Cl$: C, 62.12; H, 6.16. Found: C, 62.20; H, 6.22.

α-Bromo-*p*-methylisobutyrophenone (**2a**), 87%: bp 145–146° (5 mm) [lit.[33] bp 132–133° (8 mm)].

α-Chloro-*p*-methylisobutyrophenone (**1a**), 70%: bp 118–119° (11 mm); mass spectrum[39] (70 eV) *m/e* 196.0668 (M^+) (calcd for $C_{11}H_{13}OCl$, 196.0655).

α-Bromo-*p*-chloroisobutyrophenone (**2d**), 67%: bp 150–151° (7 mm). *Anal.* Calcd for $C_{10}H_{10}OBrCl$: C, 45.90; H, 3.85. Found: C, 46.18; H, 3.83.

α-Chloro-*p*-chloroisobutyrophenone (**1d**), 31%: bp 140–141° (15 mm) [lit.[40] bp 76–79° (0.5–0.7 mm)].

α-Bromo-*m*-nitroisobutyrophenone (**2f**), 51%: mp 82–84° (lit.[35] mp 85–86°].

α-Bromo-*m*-chloroisobutyrophenone (**1e**), 66%: bp 109–110° (0.9 mm). *Anal.* Calcd for $C_{10}H_{10}OBrCl$: C, 45.93; H, 3.85. Found: C, 46.05; H, 3.93.

α-Chloro-*m*-chloroisobutyrophenone (**2e**), 82%: bp 87–88° (0.3 mm). *Anal.* Calcd for $C_{10}H_{10}OCl_2$: C, 55.32; H, 4.65. Found: C, 55.50; H, 4.79.

α-Bromo-*p*-methoxyisobutyrophenone (**1b**), 19%: bp 155–156° (2.5 mm). *Anal.* Calcd for $C_{11}H_{13}OBr$: C, 51.38; H, 5.09; Br, 30.81. Found: C, 51.52; H, 5.10; Br, 30.87.

α-Chloro-*p*-methoxyisobutyrophenone (**2b**), 74%: bp 145–146° (11 mm) [lit.[40] bp 113.5–116.5° (1.4 mm)].

α-Bromo-2,4,6-trimethylisobutyrophenone, 79%: bp 106–107° (0.8 mm) [lit.[41] bp 160–170° (24 mm)]; nmr (CCl_4) τ 3.2 (br s, 2, aryl), 7.8 (s, 9, aryl CH_3), 8.1 (s, 6, C-CH_3).

Reaction of α-Halo-2,4,6-trimethylacetophenones with TEP. Reaction of the bromo ketone **21** with TEP (1.25 equiv) at 130° for 24 hr gave the ketophosphonate **23** (55%): bp 148–149° (0.24 mm) [lit.[30] bp 170° (0.5 mm)]; nmr (CCl_4) τ 3.2 (m, 2, aryl), 5.9 (quint, 4, CH_2CH_3), 6.75 (d, 2, CH_2P, J_{PH} = 22 Hz), 7.8 (s, 9, aryl CH_3), 8.7 (t, 6, CH_2CH_3). Similar reaction of the chloro ketone **22** at 100° for 24 hr and at 130° for 48 hr gave **23** (50%): data as above. Reaction of **21** and **22** (0.001 mol) in competition for TEP (0.001 mol) at 100° for 144 hr led to recovery of 100% of **22** and 58% of **21** by vpc; *i.e.*, 42% of **21** reacted to give **23**.

Kinetic Measurements. All materials used were freshly dried and distilled through spinning band or silver-jacketed Vigreux columns. Equimolar amounts of phosphite and halo ketone in benzene or benzonitrile at final concentrations of *ca.* 0.5–0.9 *M* were added under nitrogen *via* calibrated pipets or syringes to a long-necked glass-stoppered flask equipped with a stopcock-containing side arm. The flask had reached thermal equilibrium in a stirred thermostated bath utilizing "Teresso" oil. Solvents such as $CDCl_3$ or CCl_4 could not be used since the separation of the halo ketone methyl singlet and the product methyl doublets was incomplete. Solutions less than *ca.* 0.4 *M* in starting compounds could not be accurately measured by this method. A known amount of toluene (or, in some cases, anisole) was added (by weight) as an internal standard.

Aliquots were removed at appropriate intervals of time, TMS was added, and the sample was immediately examined by nmr spectrometry in a Varian A-60A spectrometer. For fast reactions, the aliquot was chilled to 0° upon removal from the reaction flask. No change in peak areas was seen during the nmr scanning, which was done at ambient temperature. The nmr scanning was done at 250 Hz full scale for the limited range covering the methyl singlets of the standard and halo ketone and the two doublets of the product vinyl phosphate which appeared (in the solvents used) on both sides of the halo ketone methyl singlet. Observed integrated areas of the standard and halo ketone singlets at or near zero time agreed with the calculated ratios to *ca.* ±2%. Plots of $x/(a - x)$ *vs.* time were constructed utilizing the concentration of product which had been related to the concentration of internal standard by comparison of integrated areas.[42] These plots gave straight lines by visual fitting to 50–75% of reaction. They usually went through the graph's origin. At least six measurements were taken for each run which was done at least in duplicate. All of the data in the tables are based on the appearance of vinyl phosphate. Rate constants for the reactions in Tables II and V were also calculated utilizing the disappearance of halo ketone. They are in reasonable agreement with the given data. Full nmr spectra were run for each reaction to show that vinyl phosphate was the only product formed. In the study of the effect of added acid, a similar procedure was used with a standard solution of phosphite in benzene added to a solution containing halo ketone, toluene, and acetic acid in benzene. Activation parameters were calculated using a least-squares method for each temperature. Agreement between the parameters for different temperatures was excellent and the data for 44.9° only are given in Table VI.

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