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REACTIONS OF TRIETHYL PHOSPHITE WITH ACTIVATED OLEFINS[1,2]

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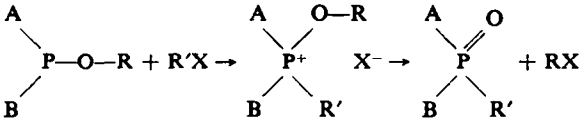
Abstract—Reaction of triethyl phosphite with a series of α,β-unsaturated esters, ketones, aldehydes, amides and nitriles in protonating solvents proceeds smoothly to furnish β-substituted phosphonate esters. This process, termed hydrophosphinylation, is quite general in contrast to reduction and reductive dimerization, the alternative reaction pathways previously observed for dibenzoylethylene. The most active olefins (methyl vinyl ketone, crotonaldehyde, cinnamaldehyde) are transformed even at 0° to furnish analogous products, predominantly in the form of their acetals or ketals. Evidence bearing on the mechanism of these transformations, particularly that concerning the site of initial attack, the origin of acetal and ketal, and the role of the solvent is discussed.

THE Michaelis–Arbuzov reaction,[3] described by Michaelis and Kaehne[4] in 1898 and explored in detail by the Arbuzov school,[5,6] involves interaction of a P(III) ester with an alkyl halide to furnish a P(V) compound, most commonly a phosphonate or phosphinate ester or a phosphine oxide (Eq. 1). Not until the upsurge of interest in



(1)

organophosphorus chemistry, stimulated by the publication of Kosolapoff's book on the subject in 1950,[6] did it become evident that this transformation was an example of a much more general phenomenon. To date more than twenty reactions have been reported for which there have been proposed similar two step mechanisms, i.e. initial nucleophilic attack by a trivalent phosphorus ester to form a quaternary alkoxyphosphonium intermediate, followed by dealkylation (SN1 or SN2) accompanied by valency expansion of phosphorus to form a P=O bond. This latter process which represents a valence shell expansion of phosphorus from 8 to 10 electrons is made possible by the availability of low energy vacant 3*d* orbitals and appears to be an important and unique aspect of phosphorus chemistry. Transformations of this type entered into by sulfonate esters, disulfides, molecular halogens, Mannich base salts, thiocyanates, lactones, etc. were recently reviewed by Harvey and DeSombre.[3]

[1] This research was supported by a research contract (SA-43-ph-1759) from the National Cancer Institute, United States Public Health Service.

[2] Presented in part before the 144th National Meeting of the American Chemical Society, Los Angeles, Calif., March, 1963.

[3] R. G. Harvey and E. R. DeSombre in *Topics in Phosphorus Chemistry* Vol. 1 (Edited by M. Grayson and E. Griffith) p. 57. Interscience, New York, N.Y. (1964).

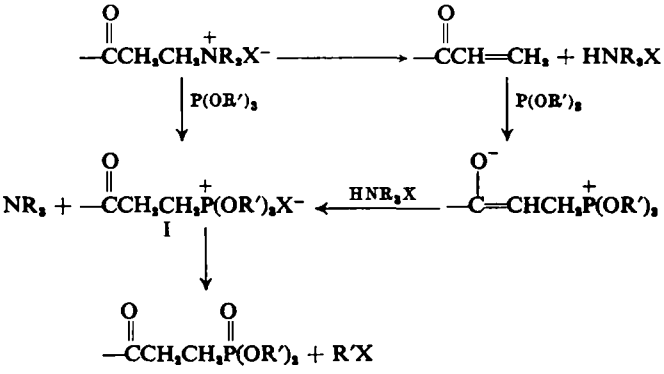
[4] A. Michaelis and R. Kaehne, *Chem. Ber.* **31**, 1048 (1898).

[5] A. E. Arbuzov, *J. Russ. Phys. Chem. Soc.* **38**, 687 (1906).

[6] G. M. Kosolapoff, *Organophosphorus Compounds*. Wiley, New York (1950).

In an earlier investigation[7] we described the synthesis of γ-ketophosphonate esters via interaction of trialkyl phosphite esters with Mannich base methiodides and hydrochlorides, and tentatively proposed an analogous two-stage nucleophilic displacement-ionic valency expansion mechanism (Chart 1). However, as pointed out in a subsequent

CHART 1



paper,[8] the same intermediate (I) may arise indirectly via elimination of the nitrogen function from the Mannich base,[9] followed by attack of the phosphorus reagent at the terminal carbon of the resulting conjugated system, and abstraction of a proton from the amine hydrohalide (Chart 1).

We were prompted, therefore, to explore the possibility that olefins susceptible to nucleophilic attack could engage in this latter type of reaction in the presence of suitable proton donors. The overall process may be termed *hydrophosphinylation*, in preference to *phosphinylation*, the less descriptive term previously employed. The observation of 1,4-addition of trialkyl phosphites to α,β-unsaturated carboxylic acids by Kamai and Kukhtin[3,10] provided support for this concept.

Our initial studies, published in preliminary form,[11] were carried out with *trans*-1,2-dibenzoylethylene (DBE) as the olefinic component. Depending upon the nature of the substituents on phosphorus, the concentration of the olefin, and the acidity of the media, DBE can participate in three general types of reaction processes, all of which take place readily at room temperature. In addition to the predicted *hydrophosphinylation* there may occur *reduction* to form 1,2-dibenzoylethane or *reductive dimerization* yielding *meso* and *d,l* forms of 1,2,3,4-tetrabenzoylbutane.

This complexity of reaction has proven to be the exception rather than the rule. In the present paper we report studies with a series of olefins activated by electron-withdrawing substituents (—CHO, —$COCH_3$, —CO_2Et, —$CONH_2$, —CN). These alkenes react smoothly with phosphite esters in protic solvents (alcohol or phenol) to

[7] T. C. Myers, R. G. Harvey and E. V. Jensen, *J. Amer. Chem. Soc.* **77**, 3101 (1955).

[8] S. Hirai, R. G. Harvey and E. V. Jensen, *Tetrahedron Letters*, 1123 (1963); *Tetrahedron*, **22**, 1625 (1966).

[9] J. H. Brewster and E. L. Eliel in *Organic Reactions*, Vol. VII (Ed. by R. Adams) p. 99. John Wiley, New York, N.Y. (1953).

[10] G. Kamai and V. A. Kukhtin, *Dokl. Akad. Nauk. SSSR* **109**, 91 (1956); through *Chem. Abstr.* **51**, 1827 (1957).

[11] R. G. Harvey and E. V. Jensen, *Tetrahedron Letters*, 1801 (1963).

form β-substituted phosphonate esters as the predominant and often the sole product (Eq. 2).

$$P(OR)_3 + R'CH = CHX + R''OH \rightarrow (RO)_2\overset{O}{\overset{\|}{P}}CHR'CH_2X + ROR'' \quad (2)$$

II

$R' = H,\ CH_3,\ C_6H_5,\ CO_2Et,\ CN;\quad X = CH_3CO,\ CO_2Et,\ CN,\ CHO,\ CONH_2$

The generality of this novel synthetic method is evident from the representative examples summarized in Tables 1 and 2. Standard conditions for these experiments were chosen on the basis of preliminary test reactions from which several tentative generalizations were derived: (1) reactions occur more rapidly (a) in methanol than ethanol and, (b) with triethyl phosphite (TEP) than with trimethyl phosphite; (2) where the solvent alcohol is not identical with the alcohol from which the P(III) ester is derived, partial ester exchange results in a mixed P(V) ester; (c) reactions in phenol are cleaner and result in higher yields with only minor or no contamination by products from ester exchange.

It is evident on the basis of the data in the tables that the steric demands of the trivalent phosphorus reagent (p^3 symmetry about this atom) are not especially limiting since phenyl, carbethoxy, methyl and dimethyl substituents on the β-olefinic carbon do not appreciably diminish the yield or alter the nature of the reaction under the standard conditions. When milder conditions or shorter reaction times are employed the effect of substituents is more evident. Methyl vinyl ketone reacts readily at 0°, whereas benzalacetone is unaltered in the presence of triethyl phosphite and ethanol for 48 hr at room temperature.

If the rate of the reaction is dependent upon polarization of the double bond by the activating group, the ease of the transformation should be directly related to the sequence of predicted electromeric effects, CHO > COR > CN > CO_2R > $CONH_2$, as is true for Michael addition.[12] Qualitatively, this expectation accords with observation. The most reactive acceptors, simple aldehydes and ketones such as crotonaldehyde and methyl vinyl ketone, undergo hydrophosphinylation even at 0°, and the product is obtained predominantly as its acetal or ketal. Cinnamaldehyde also furnishes a γ-ketophosphonate in the form of its diethyl acetal. However, in no instance have esters, amides or nitriles been observed to furnish any detectable amount of analogous products. The nature of the solvent-reactant affects the ketal/ketone ratio. For example, the reaction of TEP with methyl vinyl ketone in ethanol gave a 73% yield of phosphonate, exclusively as the diethyl ketal, but in phenol, this same ketone provided a 76% yield of the γ-ketophosphonate and only 15% of the corresponding diphenyl ketal. Only the reactive molecule crotonaldehyde furnished a phosphonate entirely as its diphenyl acetal. Ketalization appears to occur at an intermediate stage since the free γ-ketophosphonate in alcoholic solution shows no tendency to be thus transformed. A lesser amount of the corresponding enol ether accompanying ketal from methyl vinyl ketone or acetal from crotonaldehyde and cinnamaldehyde appears to arise from thermal decomposition of the ketal or acetal during distillation. Evidence that the enol ether is the intermediate from which the acetal or ketal is originally generated will be presented in this paper.

[12] E. Bergmann, D. Ginsburg and R. Pappo, in *Organic Reactions*, Vol. X, p. 179. John Wiley, New York, N.Y. (1959).

TABLE 1. PRODUCTS, $(RO)_2P(O)CH(R')CH_2X$, FROM REACTIONS OF TRIETHYL PHOSPHITE IN PHENOL (Eq. 2; R=Et; R'=Ph)
Conditions: Olefin (0·10 mole) + TEP (0·125 mole) + phenol (25 g) were stirred at 100° for 24 hr

R'	X	% Yield of II	B.p. (°C/mm)	n_D^t	C		H		P		Phenetole %[b]
					Calc.	Found	Calc.	Found	Calc.	Found	
H	CO_2Et	90	98/0·25[a]	$1·4302^{20°}$	45·37	45·63	8·04	8·32	13·01	12·99	100
Ph	CO_2Et	50	140/0·15[c]	$1·4872^{25°}$	57·32	57·55	7·38	7·56	9·86	9·84	103
CO_2Et	CO_2Et	93	140/0·05[d]	$1·4392^{28°}$	46·45	46·47	7·47	7·43	9·98	10·05	100
Ph	$COCH_3$	89	150/0·04[e]	$1·4985^{25°}$	59·14	59·63	7·45	7·06	10·90	11·08	102
H'	$COCH_3$	76	96/0·15[g]	$1·4345^{28°}$							
CH_3	CHO	82	174–84/0·12[f]	$1·5180^{28°}$	63·48	64·13	7·19	7·72	8·19	8·93	12
H	$CONH_2$	85	(m.p. 74·5–76·2)[h]	—	40·18	39·58	7·71	7·61	14·81	14·99	70
H	CN	83	110/0·10[i]	$1·4382^{20°}$							

[a] Reported b.p. 151°/10 mm[18] and 123·4/3 mm, n_D^{20} 1·4310.

[b] Identified in each case by IR spectrum of sample obtained from gas chromatography on an 8′ × 1/4″ column of 20% Ucon 20 on Chromosorb W at 200°.

[c] Reported b.p. 199–200/11 mm, n_D^{20} 1·4917.[19]

[d] Reported b.p. 161°/2 mm, n_D^{20} 1·4410.[20]

[e] Reported b.p. 203°/16 mm, n_D^{20} 1·5050.[17]

[f] Standard conditions were not employed. Instead the reactants were stirred at 0° for 3 hr.

[g] Reported b.p. 96–8/0·14 mm, n_D^{25} 1·4352.[7] There was also obtained a 15% yield of the corresponding diphenyl ketal ($n_D^{27·5°}$ 1·4151) identified by IR spectrum and by conversion to the ketone by boiling in methanolic HCl for 3 hr.

[h] Recrystallized from benzene.

[i] Physical properties and spectra were in agreement with those of an analyzed sample prepared by the method of Pudovik and Arbuzov.[17]

[j] Product was obtained as a diphenyl acetal.

[13] G. Kamai and V. Kukhtin, *Dokl. Akad. Nauk. SSSR* **112**, 868 (1957); through *Chem. Abstr.* **51**, 13, 742 (1957).

[14] W. Reppe *et al.*, Liebig's Ann. **601**, 84 (1956).

[15] [a] E. R. DeSombre, Dissertation, University of Chicago (1963); [b] E. R. DeSombre, R. G. Harvey and E. V. Jensen, *Abstr. of Papers, 146th Meeting Amer. Chem. Soc.*, Denver, Colorado, 1964, p. 216.

[16] That the dimethyl rather than the methyl ethyl ketal was obtained is not inconsistent with the hypothesis since alkoxy exchange between the medium and an intermediate related to IX is probable. For example, the dimethyl ester of 1-phenyl-3-oxobutylphosphonate is the major product from interaction of TEP with benzalacetone in methanol.

[17] A. N. Pudovik and B. A. Arbuzov, *Dokl. Akad. Nauk SSSR* **73**, 327 499 (1950).

[18] A. E. Arbuzov, T. Konstantinova and T. Antsyfrova, *Izvest. Akad. Nauk. SSSR, Otd. Khim. Nauk.* 179 (1946).

[19] A. N. Pudovik, *Zh. Obshch. Khim.* **22**, 462 (1952).

[20] A. N. Pudovik, *Izv. Akad. Nauk. SSSR, Otd. Khim. Nauk.* 926 (1952); *Chem. Abstr.* **47**, 10, 467 (1953).

TABLE 2. PRODUCTS, $(RO)_2P(O)CH(R')CH_2X$, FROM REACTIONS OF TRIETHYL PHOSPHITE IN EtOH (Eq. 2; R,R″ = Et)
Conditions: The olefin and TEP were stirred at reflux temp in EtOH for 24 hr, except where otherwise specified.

R′	X	Olefin (moles)	TEP (moles)	EtOH	% Yield of II[a]	b.p. (°C/mm)	n_D^t	C Calc.	C Found	H Calc.	H Found	P Calc.	P Found
H	CO_2Et	0·20	0·20	10 ml	50	96/0·3	$1·4302^{30°}$	45·37	45·63	8·04	8·32	13·01	12·99
H	$COCH_3$[b]	0·20	0·20	0·8 mole	[73]	118/0·25	$1·4356^{24°}$	—	—	—	—	—	—
CH_3	CHO[c]	0·25	0·25	1 mole	[59][d]	99/0·05	$1·4320^{30°}$	51·05	51·32	9·64	9·74	10·97	11·31
Ph	CHO	0·25	0·25	1 mole	[61]	148/0·05	$1·4831^{26.5°}$	59·29	59·30	8·49	8·35	9·00	9·14
H	$CONH_2$	0·20	0·25	0·53 mole	42[e]	(m.p.75–76°)	—	—	—	—	—	—	—
H	CN	0·50	0·60	1·32 mole	44	96/0·05[f]	$1·4370^{25°}$	—	—	—	—	—	—
CN	CN	0·10	0·10	50 ml	55	135/0·005[g]	$1·4432^{28°}$	44·44	43·84	6·06	6·30	14·33	14·27

[a] Brackets indicate product obtained as diethyl acetals or ketals.

[b] The TEP was added over 25 min to a solution of the olefin in ethanol at 0°, stirred at this temp for a total of 1 hr and distilled. The product, which was contaminated with the corresponding ketone and enol ether, was converted to the ketone by boiling with methanolic HCl.

[c] The TEP was added to a stirred solution of crotonaldehyde in EtOH and maintained at 0° for 1 hr. The solution was allowed to warm to room temp; after 3 hr more the mixture was heated at reflux to give a total reaction time of 24 hr.

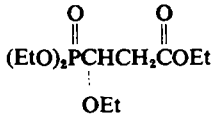
[d] There was also obtained the corresponding ethyl enol ether (19%; b.p. 120/0·25; $n_D^{20°} = 1·4472$; reported b.p. 136–138/1 mm, $n_D^{20°} = 1·4506$[18]. On mild hydrolysis the enol peak at 6·08 μ disappeared and was replaced by a carbonyl absorption at 5·80 μ; preparation of a 2,4-dinitrophenylhydrazone derivative directly from the enol ether was unsuccessful.

[e] Two other products, II (R = Et; R′ = CN) and II (R = Et; R′ = H; X = CONHEt) in yields of 8 and 19%, respectively, were also obtained.

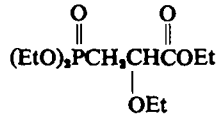
[f] Reported b.p. 159–160/10 mm, $n_D^{20} = 1·4388$[17]. Polyacrylonitrile (34%) was the other major product.

[g] Pressure gauge not reliable at this range.

Acetylenic acceptors, judging by the behaviour of ethyl propiolate, are more reactive than the corresponding olefins, since this ester underwent reaction with TEP in ethanol at 0°. In the case of ethyl propiolate the major product showed no evidence of a double bond in its IR spectrum, and analytical data were in agreement with the incorporation of an additional molecule of ethanol into the expected structure. Hydrolysis converted it into a tribasic acid still containing the elements of ethanol. The only structures compatible with the spectral properties, analytical data and chemical behavior are the ethers III and IV.



III



IV

The NMR spectrum (Table 3) of the tribasic acid derived from this ester exhibits a quartet at τ 6·60 (J = 7) and a triplet at τ 9·33 (J = 7) for the ether methylene and methyl, respectively, an apparent quintet at τ 5·95 (J = 7) for the methine proton, and a doublet of doublets centered at τ 6·28 for the remaining methylene. The complex splitting pattern of the methine and adjacent methylene protons is in satisfactory accord with the structure of this acid's precursor being III. The methine signal (H_B of an A_2BX system) should be split into a triplet by the adjacent methylene with each peak split again by coupling with phosphorus. The observed quintet arises from partial overlapping of the predicted triplets at τ 5·83 and 6·08 (J_{HH} = 7 and J_{PH} = 16 c/s). Coupling with H_B and phosphorus should split the H_A signal into a doublet of doublets. These were observed at τ 7·81 and 8·10 (J_{HH} = 7 and J_{PH} = 17 c/s). The NMR spectrum of the corresponding triester, III, was less revealing due to concealment of the methine proton under the absorption due to phosphorus ester methylene in the region τ 5·90. However, the doublet of doublets expected for CH_2 bound to CH was clearly revealed at τ 7·61 and 7·91 (J_{HH} = 7 and J_{PH} = 18 c/s).

Interaction of acrylamide with TEP in ethanol furnished two minor products in addition to diethyl 2-carbamylethylphosphonate. These were identified as diethyl 2-cyanoethylphosphonate, previously obtained from hydrophosphinylation of acrylonitrile, and II (R = Et; R′ = H; X = CONHEt), the N-ethyl derivative of the major product. The structure of the latter is supported by microanalysis, IR (amide I and II bands at 1655 and 1555 μ respectively) and NMR data (Table 3). The single broad amide proton resonance at τ 4·87 contrasts strongly with the two broad peaks at τ 3·70 and 3·03 exhibited by the related primary amide.

The essential role of the solvent as a participant in these transformations is borne out by the recovery of phenetole (Eq. 2; R″ = Ph) in quantities somewhat greater than those of the major (non-acetal or ketal) product. This discrepancy results from the yield of phenetole, which is based upon gas chromatographic analysis, being more accurate than that of the phosphonate which is reported as the percentage of pure compound actually isolated. Only for acrylamide did phenetole recovery (70%) fall below that of the phosphonate, diethyl β-amidoethylphosphonate (85%); repetition confirmed these figures. In the absence of a protic solvent, reaction generally fails to take place. For example, benzalacetone and TEP heated in phenol at 100° for 24 hr furnished diethyl 1-phenyl-3-oxobutylphosphonate (89%), whereas attempted

TABLE 3. NMR DATA[a] FOR PHOSPHONATE ESTERS, $RPO(OEt)_2$

R	Phosphorus ester CH_2	Phosphorus ester CH_3	Carbon ester CH_2	Carbon ester CH_3	CH_2CO	Other
$EtO_2CCH_2CH_2$	5·90 qu $J_{HH} = J_{PH} = 7$	8·68 t J = 7	5·83 q J = 7	8·75 t J = 7	7·1–8·4 m	$(CH_2—P)$7·1–8·4 m
$EtOCCH_2CHOEt$[c]	5·88 m[b]	8·78 t J = 7	5·85 m[b]	8·72 t J = 7	7·61 d, 7·91 d $J_{HH} = 7$, $J_{PH} = 18$	$(CH_2—O)$6·20–6·66 m; (CH_3)8·72 t J = 7
HO_2CCH_2CHOEt[c,d]					7·81 d, 8·10 d $J_{HH} = 7$, $J_{PH} = 17$	$(CH_2—O)$6·60 q; J = 7; (CH_2)9·33 t; J = 7; (CH)5·83 t, 6·08 t $J_{HH} = 7$, $J_{PH} = 16$
EtO_2CCH_2CHPh	5·73–6·66 m[b]	8·95 t, 8·78 t J = 7, 7	5·73–6·66 m[b]	8·78 t J = 7	6·94 d, 7·10 d $J_{HH} = 7$, $J_{PH} = 14$	(Ar)2·72
$H_2NCOCH_2CH_2$	5·90 qu $J_{HH} = J_{PH} = 7$	8·68 t J = 7				(NH_2)3·70 s, 3·03 s
$EtNHCOCH_2CH_2$	6·00 qu $J_{HH} = J_{PH} = 7$	8·83 t J = 7			7·50–8·16 m	(NH)4·80 s; $(CH_2—P)$7·66–8·67 m $(CH_2—N)$6·64 qu; (CH_3)8·87 t J = 6·5 J = 7
$CH_3COCH_2CH_2$	5·87 q, 6·04 q J = 7, 7	8·72 t J = 7			7·83–8·38 m	(CH_3CO)8·38 s; $(CH_2—P)$7·00–7·55 m
CH_3COCH_2CHPh	5·70–6·58 m[b]	8·93 t–8·75 t J = 7, 7			6·78 d, 6·96 d $J_{HH} = 7$, $J_{PH} = 18$	(CH_3CO)7·96 s (Ar)2·72

[a] Spectra taken in $CDCl_3$; splitting pattern (s = singlet, d = doublet, t = triplet, q = quartet, qu = quintet, m = multiplet) indicated after chemical shifts expressed in τ units relative to tetramethylsilane; the coupling constants, J, are in c/s.

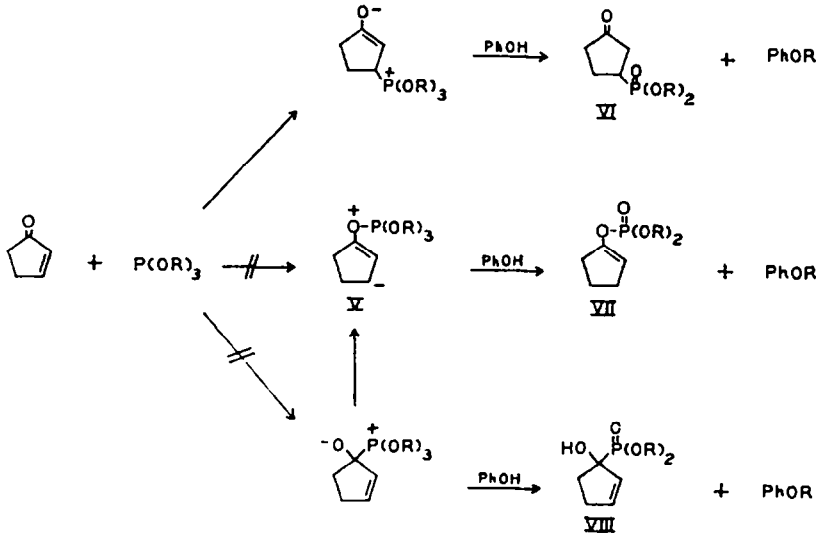
[b] The methine proton is obscured by this multiplet.

[c] The peak at τ 7·65 in the ester and those at τ 8·16 and τ 7·87 in the acid exhibited additional splitting with J = 2·4, 1·2, and 2·0 c/s, respectively.

[d] Data are for the tribasic acid in D_2O.

repetition in dioxane rather than phenol led only to recovery of unchanged starting materials. A notable exception is found with α,β-unsaturated aldehydes which are sufficiently reactive to interact with phosphite even in aprotic medium. However, this combination takes a different course, and we have not studied it except to confirm the report of Kamai and Kukhtin[13] that reaction of crotonaldehyde with TEP neat gave the ethyl enol ether of β-(diethoxyphosphinyl)butyraldehyde in low yield as the sole isolable product after distillation.

The assumption that hydrophosphinylation proceeds via the sequence, nucleophilic attack by phosphite at the terminal carbon atom of the conjugated system, protonation, and ionic valency expansion of phosphorus is in agreement with all the experimental observations. The alternative possibility that initial attack on the π electron system by the non-bonding electrons on phosphorus takes place on the carbonyl oxygen with later transfer to β carbon via a ring intermediate[11] is worthy of consideration. 2-Cyclopentenone in which the restricted geometry of the intermediate (V) should effectively prevent such transfer reacts normally with TEP in phenol to furnish only the 3-ketocyclopentylphosphonate ester (VI) and none of the enol phosphate ester (VII) or the

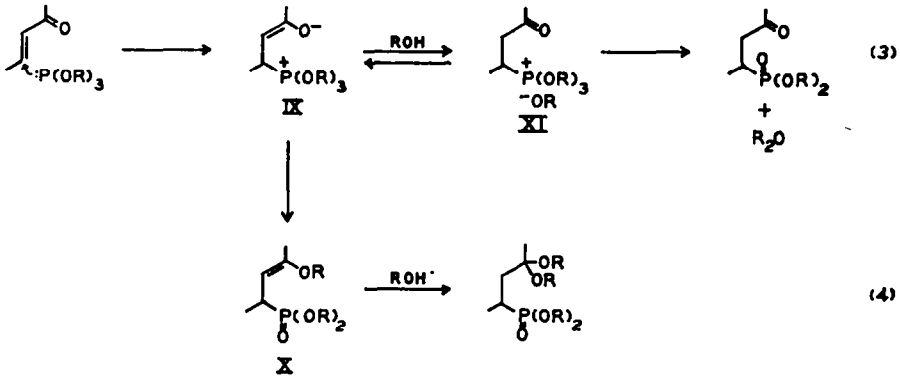


hydroxyphosphonate ester (VIII). Moreover, progesterone (in which the β-carbon is relatively hindered) showed no tendency to react under standard conditions in ethanol. It is reasonable to assume, therefore, that attack by phosphorus is exclusively at the terminal carbon of the conjugated system and that a similar mechanism holds for the majority of acceptors.

Less certain, however, is the origin of ketal and acetal. With TEP and ethanol only the more active olefins provide this type of product, and only these same olefins appear to be capable of interacting with phosphite esters in the absence of a protic solvent. Since in these latter instances the product is obtained as the related enol ether,[13] it is conceivable that under the standard conditions employed ketal and acetal arise by addition of alcohol to enol ether. This hypothesis was confirmed by the finding that the enol ether of diethyl 3-oxobutylphosphonate refluxed in absolute alcohol for 1 hr underwent loss of the 6·00 μ (C=C) absorption in the IR with concomitant appearance

of broad ketal peaks in the 8·90–9·50 μ region, and no significant alteration of other major peaks (except for the appearance of a small 5·72 μ band indicative of a minor proportion of free ketone). thus indicating virtually complete conversion to the related ketal. Transformations of this type normally require acidic catalysis;[14] since in this instance the medium was essentially neutral, it seems likely that the dialkoxyphosphinyl group may be intimately involved in ketal formation.

There remains also the problem of why the more active alkenes furnish products predominantly through a pathway via enol ether to acetal (Eq. 4) in preference to the more direct route of protonation and valency expansion (Eq. 3). Several additional facts are pertinent. First, diethyl 3-oxobutylphosphonate was recovered unchanged from its solution in refluxing absolute alcohol (with or without TEP present), indicating that γ-keto ester is not the precursor of γ-ketal ester. Secondly, the diethyl ketal of this same compound was similarly unaffected by boiling in alcohol, evidence that the converse is also true. Thirdly, factors which favor reaction under gentle conditions, namely use of methanol rather than ethanol, and phosphonite or phosphinite rather than phosphite esters, permit ketal formation even with the less active unsaturated ketones related to chalcone.[15] Finally, although enol ether formation may conceivably occur by intramolecular valency expansion of IX, in its simplest form this requires an unfavorable seven-membered ring, and in at least one case where steric restrictions severely hinder intramolecular valency expansion, ketal formation proceeds normally. Reaction of 2-cyclopentenone with ethyl diphenylphosphinite in methanol[15] furnished a 78% yield of the ketal[16] of diphenyl 3-oxocyclopentylphosphine oxide. It is therefore necessary to postulate that this step be intermolecular, involving either two molecules of IX, or, as suggested by a referee, a molecule each of protonated IX and IX itself.



The simplest hypothesis consistent with all of these facts is that for the majority of olefins protonation-valency expansion (Eq. 3) of the trialkoxyphosphonium intermediate related to IX proceeds at a rate greater than loss of IX via the alternate pathway to enol ether (Eq. 4). If, as appears likely, valency expansion of IX to furnish X is intermolecular, this process should provide important competition when concentration of IX becomes appreciable; this condition should be favored by factors which increase the rate of initial nucleophilic attack to form IX, namely, activation of the olefinic double bond by a strongly polarizing substituent (e.g. CHO), or enhancement of the nucleophilicity of the phosphorus reagent by attachment of appropriate groups to phosphorus. The latter effect is apparently responsible for the increasing

ketal/ketone ratio in the series phosphite–phosphonite–phosphinite.[15] Finally, consideration of the equilibrium IX $\rightleftarrows$ XI, evidently dependent upon the protonating ability of the solvent, leads to expectation of a higher proportion of free ketophosphonate from reaction in phenolic vs. alcoholic media.

It is noteworthy that the alternative processes of reductive dimerization and reduction previously described for *trans*-1,2-dibenzoylethylene[11] were not observed for other symmetrical negatively substituted olefins (diethyl fumarate or fumaronitrile). Further studies of this specific problem will be reported separately.

The synthetic utility of hydrophosphinylation of olefins with P(III) esters in alcohol appears superior to either the Kamai reaction[13] or the Pudovik synthesis.[17] The former, which differs from the present reaction by the omission of a protonating solvent, is limited to the more active olefins and furnishes the product in low yield in the form of its enol ether. The Pudovik reaction in which, for example, the Michael type addition of sodium dialkyl phosphonate to methyl vinyl ketone furnishes dialkyl 3-ketobutylphosphonate (Eq. 5a; R′ = H) is fairly general with simple negatively substituted olefins. However, the exceptional reactivity of the phosphorus reagent, the strongly basic medium required, and the sensitivity of the reaction to steric factors limit its use.

$$(RO)_2\overset{O}{\overset{\|}{P}}H + R'_2C{=}CHC\overset{O}{\overset{\|}{H}}_3 \xrightarrow[ROH]{RONa} \begin{cases} (RO)_2\overset{O}{\overset{\|}{P}}CR'_2CH_2C\overset{O}{\overset{\|}{C}}H_3 \\ \text{XII} \\ \text{or} \\ (RO)_2\overset{OOH}{\overset{\|\ \ |}{P}}C(CH_3)CH{=}CR'_2 \end{cases} \quad (5a), (5b)$$

For example, α,β-unsaturated ketones hindered in the β-position either fail to react or, as with mesityl oxide (Eq. 5b; R′ = CH_3) undergo addition across the carbonyl; aldehydes add across the carbonyl exclusively.

EXPERIMENTAL

Physical data. M.p.'s were taken on a Leitz Kofler hot-stage microscope and are corrected. IR spectra were recorded with a Perkin–Elmer Infracord Model 137 utilizing either liquid films between NaCl plates or pressed KBr discs. Gas chromatographic analyses were performed on an F and M Model 500 instrument equipped with a thermal conductivity detector.

Materials and methods. Triethyl phosphite (TEP) supplied by the Virginia-Carolina Co., and ethyl orthoformate supplied by Eastman Kodak were redistilled and stored under N_2. The olefins and ethyl propiolate were reagent grade and were used without additional purification, except where otherwise noted. Florisil (100–200 mesh), supplied by the Floridin Co., was activated overnight in an oven at 100° prior to use in column chromatography. *The procedure employed for the hydrophosphinylation of ethyl acrylate may be taken as representative for the examples of this transformation in Tables* 1 *and* 2 *which are not described explicity in the following paragraphs.*

Diethyl 2-*carbethoxyethylphosphonate* (II: R = Et; R′ = H; X = CO_2Et) (XIII). Ethyl acrylate (Eastman) was distilled prior to use into a flask containing a small quantity of solid Na_2CO_3 and hydroquinone. A solution of this ester, TEP and phenol in the standard proportions (Table 1) was heated in an oil bath at 100° under N_2 for 24 hr. Components boiling lower than the main product were removed by distillation with gradually increasing temp to 110°/6 mm, and the phenetole content was measured by gas chromatography on an 8′ × ¼″ column of 20% Ucon 20 on chromosorb W at 200°. Phenol and phenetole were easily separated by this means and positively identified by IR spectra of samples collected in tapered glass tubes inserted in the exit port. Crude XIII (b.p. 109°/0·5

mm, 98%) obtained from distillation of the main product through a short Vigreaux column was contaminated with a small amount of an aromatic substance (absorption at 14·4 μ), possibly a phenyl ester. Redistillation through a Podbielniak Heliband column gave pure XIII.

Removal of phenol before distillation by treatment of the crude product with 10% KOH proved unsatisfactory even though the yield of crude XIII was approximately 90%, since further purification by chromatography and distillation led to considerable decomposition during distillation.

Repetition in EtOH (Table 2), followed by distillation of the product furnished XIII (50%) as well as a residue (3·53 g) which on the basis of IR spectra and microanalysis appears to be a telomer with an average of 5–6 acrylate units per phosphorus.

Overnight hydrolysis of XIII (5 g) in refluxing conc HCl furnished 2-carboxyethylphosphonic acid recrystallized from acetone (m.p. 165–167°, 3·07 g, 95%; m.p. reported 170°,[18] 165·5–167,[21] 178–180°[22]). (Found: C, 23·37; H, 4·77; P, 19·98. Calc. for $C_3H_7O_5$: C, 23·39; H, 4·58; P, 20·11.)

Diethyl 2-carbethoxy-1-phenylethylphosphonate (II: R = Et; R′ = Ph; X = CO_2Et). The product from reaction of freshly redistilled ethyl cinnamate (Matheson, Coleman and Bell) with TEP in phenol was treated with 10% KOHaq prior to distillation. This may account for the unusually low yield in this case, although this point was not checked.

2-Carboxy-1-phenylethylphosphonic acid obtained by overnight treatment of the ester with conc HCl, crystallized as a benzene-containing solvate from benzene-1,2-dimethoxyethane (m.p. 189–190·6°, 99%). (Found: C, 53·59; H, 5·46; P, 11·69. $C_9H_{11}O_5P + \frac{1}{2}C_6H_6$ requires: C, 53·54; H, 5·24; P, 11·50.) Removal of the solvent by heating this substance in an Abderhalden drying pistol with refluxing xylene furnished the free acid (m.p. 194–196°; reported[19] 204°). (Found: C, 47·21; H, 5·08; P, 13·44. Calc. for $C_9H_{11}O_5P$: C, 46·96; H, 4·82; P, 13·46.)

Diethyl and dimethyl 1-phenyl-3-oxobutylphosphonate (II: R = Et *and* Me; R′ = Ph, X = COMe). Hydrolysis of the diethyl ester (5 g) in refluxing conc HCl (10 ml) for 24 hr furnished a syrup which failed to crystallize for several months until triturated with dry benzene. Recrystallization from benzene–acetone provided the analytical sample of 1-phenyl-3-oxobutylphosphonic acid (m.p. 115–116·2°, 96%). (Found: C, 52·64; H, 5·67; P, 13·64. $C_{10}H_{13}O_4P$ requires: C, 52·63; H, 5·74; P, 13·58.)

The dimethyl ester of the foregoing acid was the major product (15·62 g, boiling range 123–132°/0·03 mm) obtained from interaction of benzalacetone (0·1 mole) with TEP (0·1 mole) and methanol (10 ml) maintained at reflux for 24 hr. It was identified by its IR spectrum ($\nu_{C=O}$ 5·82, $\nu_{P=O}$ 8·08, $\nu_{P=OEt}$ 8·65, ν_{POC} 9·76 μ) and its *p*-chlorobenzylthiuronium derivative,[23]

$$(QO)(MeO)PCH(C_6H_5)CH_2\overset{O}{\overset{\|}{C}}CH_3,$$

which melted at 160–161·5°). (Found: C, 51·62; H, 5·69; N, 6·16; Cl, 8·23; S, 7·40. $C_{18}H_{20}O_4ClPS$ requires: C, 51·52; H, 5·46; N, 6·32; Cl, 8·00; S, 7·24.)

Diethyl 3-oxocyclopentylphosphonate (VI: R = Et). Reaction of 2-cyclopentenone (Aldrich) with TEP under standard conditions in phenol (Table 1) furnished VI (R = Et) (b.p. 104°/0·15 mm; n_D 28° 1·4591; 72%) (Found: C, 49·22; H, 7·88; P, 14·09. $C_9H_{17}O_4P$ requires: C, 49·09; H, 7·78; P, 14·07), and phenetole (103%). The acid, obtained by treatment of the diethyl ester of VI with refluxing conc HCl, solidified slowly after repeated trituration with dry ether. (Found: C, 37·12; H, 5·56; P, 18·69. $C_5H_9O_4P$ requires: C, 36·59; H, 5·53; P, 18·88.)

Diethyl 3-oxobutylphosphonate (II: R = Et; R′ = H; X = $COCH_3$). Distillation of the mixture from reductive phosphinylation of methyl vinyl ketone in phenol provided the impure 3-oxobutylphosphonate; its diphenyl ketal (carbonyl and enol absorptions absent from IR spectrum; bands characteristic of P=O, POEt, POC, ketal and phenyl present at 7·95, 8·58, 9·72, 9·0–9·6 and 14·4 μ, respectively), remained as the distillation residue. The contaminant in the ketoester was demonstrated to be phenol by vapor phase chromatography on a 6′ × ¼″ column of 2% Versamid on Chromosorb W programmed from 125° at 5°/min giving retention times of 7·6 and 12·2 min for phenol and the ester, respectively. Pure ketoester was obtained by chromatography of the main distillation product on dry Florisil by elution with 1:1 ether–pentane; its IR absorption spectrum ($\nu_{C=O}$ 5·80, $\nu_{P=O}$ 8·00, ν_{POEt} 8·58, and ν_{POC} 9·68 μ) and refractive index were in agreement with those of an authentic sample.[7]

[21] H. W. Coover, Jr., M. A. McCall and J. B. Dickey, *J. Amer. Chem. Soc.* **79**, 1963 (1957).
[22] P. Nylen, *Ber. Dtsch. Chem. Ges.* **59**, 1119 (1926).
[23] R. G. Harvey and E. V. Jensen, *J. Org. Chem.* **28**, 470 (1963).

The diphenyl ketal, boiled for 3 hr in MeOH acidified with a drop of conc HCl, was converted to ketone which was identified by its IR spectrum after recovery of it and phenol from gas chromatography on a 2% Versamid column.

Diethyl 1,1-*dimethyl*-3-*oxobutylphosphonate* (XII: R = Et; R′ = CH_3). Distillation of the product from reaction of mesityl oxide with TEP in phenol under standard conditions provided XII (b.p. 98/1·6 mm; n_D 28° 1·4384; 96%). (Found: C, 50·76; H, 9·04; P, 12·80. Calc. for $C_{10}H_{21}O_4P$: C, 50·84; H, 8·96; P, 13·11.)

Diethyl and diphenyl acetals of diethyl 3-*oxo*-1-*methylpropylphosphonate* (II: R = Et; R′ = CH_3; X = CHO). These acetals, obtained from interaction of crotonaldehyde with TEP in phenol and ethanol, respectively, were characterized by microanalysis, IR spectra, hydrolysis to the free aldehyde, and by their 2,4-dinitrophenylhydrazone derivatives. The latter was obtained directly from the diethyl acetal as yellow needles (m.p. after 2 recrystallizations from cyclohexane 120·5–121·5°; 85%). (Found: C, 43·39; H, 5·60; N, 14·50; P, 7·83. $C_{14}H_{21}O_7N_4P$ requires: C, 43·29; H, 5·45; N, 14·43; P, 7·98.)

Diethyl acetal of diethyl 3-*oxo*-1-*phenylpropylphosphonate* (II: R = Et; R′ = Ph; X = CHO). This acetal (10 g), the sole product from reaction of TEP with benzalacetone in ethanol, underwent hydrolysis in a solution of 25 ml water, 100 ml acetone and 1 ml conc HCl maintained at reflux for 90 min to furnish the free aldehyde ($\nu_{C=O}$ 5·79 μ) contaminated with what is probably a condensation product ($\nu_{C=O}$ 5·98 μ). From 2·7 g of the hydrolysate there was obtained 3·27 g of the 2,4-dinitrophenylhydrazone of diethyl 3-oxo-1-phenylpropylphosphonate (m.p. 141–142°). Recrystallization from benzene–cyclohexane provided the analytical sample (m.p. 165–166°). (Found: C, 51·29; H, 5·52; P, 6·71. $C_{19}H_{23}O_7N_4P$ requires: C, 50·67; H, 5·15; P, 6·88.)

Diethyl 2-*carbamylethylphosphonate* (II: R = Et; R′ = H; X = $CONH_2$). The product from treatment of acrylamide (0·2 mole) with TEP in phenol was subjected to steam distillation to remove phenetole and part of the phenol, and the residue was extracted with benzene, then with methylene chloride. A total of 14 more extractions were required to lower the weight of product recovered per extraction to 200 mg. The extract were dried ($MgSO_4$) and evaporated to a crystalline oily residue. Trituration with ether followed by crystallization from benzene provided the pure amide. The ether solution and the mother liquors were concentrated and chromatographed on Florisil to provide in addition to phenol (865 mg) and a further crop of the amide (eluted with 1:1 acetone–ether) a small quantity (200–250 mg) of the related nitrile (II: R = Et; R′ = H; X = CN).

A similar reaction in ethanol led, after removal of the more volatile components under reduced pressure, to 40 g of an oil separated by chromatography on Florsil into the three major components in Table 2: the β-carbamyl and cyano phosphonates (eluted with 30% acetone in ether and acetone, respectively) and an oil eluted by 40–80% acetone in ether with n_D^{26} 1·4512 and absorptions in the IR characteristic of a secondary amide structure[24] (2·91, 3·04, 3·27, 6·04 (amide I), 6·43 (amide II), and 7·72 μ) as well as the diethoxyphosphinyl group (8·00, 8·62 and 9·65 μ). This absorption pattern along with microanalysis and NMR data are reasonably good evidence for the N-ethyl derivative II (R = Et; R′ = H; X = CONHEt) as the structure of this substance. (Found: C, 44·75; H, 8·35; N, 5·86; P, 12·47. $C_9H_{20}O_4NP$ requires: C, 45·56; H, 8·50; N, 5·91; P, 13·06.)

Diethyl 1-*ethoxy*-2-*carbethoxyethylphosphonate* (III). TEP (33·23 g, 0·2 mole) was added over a period of 3 hr to an ice-cold, rapidly stirred solution of ethyl propiolate (19·62 g, 0·2 mole) in 50 ml ethanol. After 2 hr at 0°, the solution was allowed to warm to room temp and stirring was continued for a total period of 19 hr. The color of the solution passed through green and yellow while cold, and finally became port red. Distillation furnished III (b.p. 132°/0·25 mm; n_D 24·5° 1·4352; 38%). (Found: C, 47·61; H, 8·47; P, 10·88. Calc. for $C_{11}H_{23}O_6P$: C, 46·80; H, 8·21; P, 10·97.)

Hydrolysis of the ester (5 g) in 10 ml refluxing conc HCl for 24 hr provided the free acid (3·51 g) as a syrup which slowly crystallized. Recrystallization from chloroform–acetone gave the analytical sample (2·66 g, 76%, m.p. 120–121·5°). (Found: C, 30·37; H, 5·80; P, 15·60. Calc. for $C_6H_{11}O_6P$: C, 30·31; H, 5·60; P, 15·64.)

Ethyl enol ether of diethyl 3-*oxobutylphosphonate*. A solution of diethyl 3-oxobutylphosphonate (28·23 g, 0·1 mole), ethyl orthoformate (30 ml), and *p*-toluenesulfonic acid (100 mg) in 50 ml dry benzene were maintained at reflux under N_2. Periodically, 5 ml samples were removed, quenched in an equal volume of 5% $NaHCO_3$aq, washed with water, dried (Na_2SO_4), and examined by comparison of the C=O and C=C band intensities in the IR at 5·82 and 6·00 μ, respectively. After 5 hr,

[24] K. Nakanishi, *Infrared Absorption Spectroscopy*. Holden-Day, San Francisco (1962).

reaction having apparently ceased short of completion, another 150 mg of the acid catalyst was added and heating was resumed for an additional 16 hr. Distillation furnished the enol ether (b.p. 102°/0·2 mm) slightly contaminated with the ketone as evidenced by a weak absorption at 5·82 μ

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