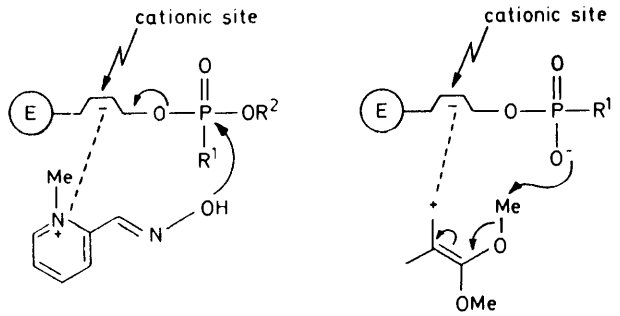
The Nucleophilic Reactivity of Organophosphorus Compounds. Part 4.† The Alkylation of Phosphorus Acid Anions with 'Onium Keten Acetals

By **Alexander T. Zaslona** and **C. Dennis Hall,*** Department of Chemistry, King's College, University of London, Strand, London WC2R 2LS

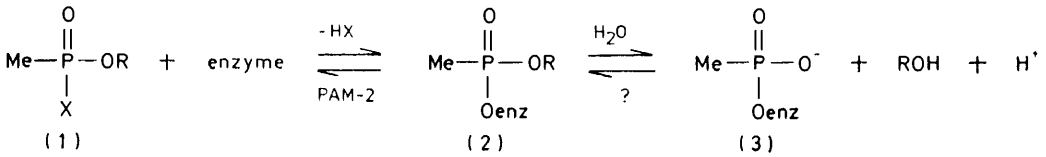
The preparations of phosphonium and pyridinium keten acetals are reported and their reactions with a variety of phosphorus acid anions are described. The novel pyridinium keten acetals are useful reagents for the alkylation of various acid anions in aprotic, aqueous and aqueous-emulsion media.

PREVIOUS work in this area has shown that phosphorus acids react with keten acetals in aprotic media to give high yields of phosphorus esters.[1-3] The mechanism of this reaction involves a fast reversible protonation of the keten acetal, followed by nucleophilic attack by the phosphorus acid anion on the intermediate carbocation.[3] This is in marked contrast with the hydrolysis of keten acetals, which is a general acid-catalysed reaction involving rate-determining protonation of the acetal.[4] The objective of this work was to provide a means of alkylating 'aged', phosphorus-inhibited acetylcholinesterase (3) and hence to regenerate the phosphorylated enzyme (2) which would be susceptible to conventional oxime (PAM-2) therapy (Scheme 1).[5]

In this respect the conventional keten acetals proved to be ineffective presumably since, under physiological conditions, the rate-limiting step for the keten acetals (protonation) was followed by a rapid and totally indiscriminate attack by the surrounding nucleophiles, the bulk of which would be water. Hence it was reasoned that in order to achieve re-alkylation of aged, inhibited enzyme one would need an alkylating agent that (*i*) was fairly stable to water; (*ii*) reacted by nucleophilic attack at the alkylating centre (rather than by protonation followed by nucleophilic attack); and (*iii*) would bind with the enzyme in question in order to bring the phosphorus acid anion and the alkylating agent into close proximity. It has been postulated that the superior reactivating power of PAM-2 (4) is due to interaction with the cationic site of the enzyme[6] and hence an 'onium keten acetal, *e.g.* (5), might be expected to interact in a similar manner with the enzyme-bound phosphorus acid anion. The purpose of this paper is to describe the preparation of two types of 'onium keten acetals and their reactions with phosphorus acids and phosphorus acid anions under aprotic, aqueous, emulsion, and phase-transfer conditions. It was considered that the latter two conditions might provide better models for the *in vivo* interaction between inhibited acetylcholinesterase and the alkylating agent.



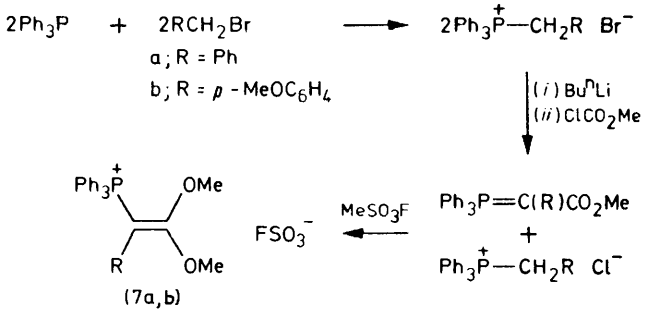
(4) E = enzyme (5)



SCHEME 1

RESULTS AND DISCUSSION

(1) *Preparation and Properties.*—(a) *Triphenylphosphonium keten acetals.* Two triphenylphosphonium keten acetals (7a,b) were prepared by the method outlined in Scheme 2. The overall yields were good (*ca.* 60%)



SCHEME 2

and the alkylation step for R = aryl, followed that reported by Bestmann [7,8] (who used Et_3O^+ BF_4^-) and gave exclusive alkylation on oxygen. With R = H, however, the ylide (8) methylated exclusively on carbon to give

† Part 3 is ref. 3*b*.

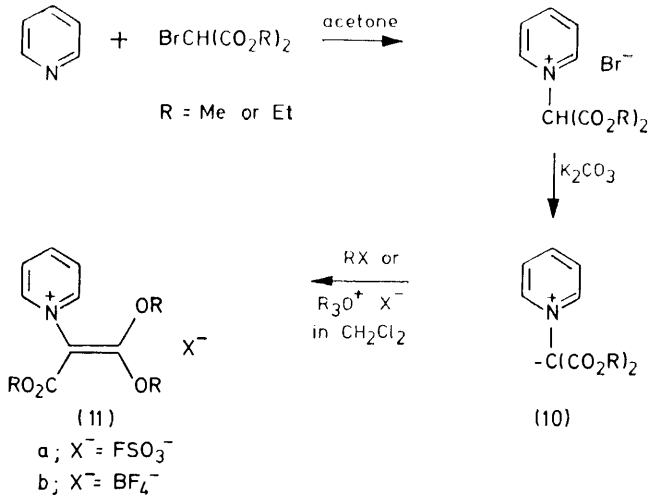
(9) with both methyl fluorosulphonate and trimethyloxonium tetrafluoroborate.

$$\underset{(8)}{Ph_3P{=}CHCO_2Me} \xrightarrow[Me_3O^+BF_4^-]{MeSO_3F\ or} \underset{(9)}{Ph_3\overset{+}{P}CH(Me)CO_2Me\ X^-}$$

$$X = SO_3F \text{ or } BF_4$$

The phosphonium keten acetals (7a,b) are insoluble in water but may be recrystallised from aqueous acetonitrile or aqueous dioxan. They are hydrolytically stable in neutral or weakly acidic media, (98% recovered after heating under reflux in 50% aqueous dioxan at pH 5.8), hydrolyse slowly to the phosphonium salt in 50% aqueous acetone at pH 1 ($t_{\frac{1}{2}}$ 2.6 h at 35 °C) and decompose in a conventional manner for phosphonium salts [9] to triphenylphosphine oxide under strongly basic conditions (aqueous dioxan at pH 13).

(b) *N-Pyridinium keten acetals.* The preparation of *N*-pyridinium keten acetals (11) was accomplished by the route shown in Scheme 3. The ylide (10; R = Et)



SCHEME 3

was readily alkylated by triethyloxonium tetrafluoroborate or ethyl fluorosulphonate in CH_2Cl_2 to give the *O*-alkylated product (11) exclusively, in yields exceeding 90%. The methyl analogue of (10), however, reacted with methyl fluorosulphonate to give mixtures (*ca.* 4 : 3) of the *O*- and *C*-alkylated material. Heating to 35 °C or prolonged standing at ambient temperature increased the amount of *C*-alkylation so that after 14 days at room temperature the ratio of *O*- to *C*-alkylated material had fallen to 2 : 3, which presumably reflects the greater thermodynamic stability of the latter product.

The keten acetals were obtained as viscous oils, which in the case of the ethyl compounds could be crystallised by trituration with dry ether. This was best achieved by using dimethyl ether at −40 °C for the less stable fluorosulphonate keten acetal, whilst the tetrafluoroborate salt crystallised using diethyl ether at ambient temperature.

The fluorosulphonate salt (11a; R = Et) was hygroscopic and hydrated rapidly when solutions in polar organic solvents were exposed to moisture. The sensitivity to moisture accounts for the poor microanalytical results on this compound even though the n.m.r. data showed the compound to be pure. The tetrafluoroborate keten acetal (11b; R = Et), however, was much more stable and could be recrystallised from water.

Both keten acetals were readily dealkylated by inorganic bases (*e.g.* K_2CO_3 or NaOH) and by organic bases (*e.g.* NaOEt, Et_3N or $PhNH_2$). Under neutral or slightly acidic conditions, however, the compounds hydrolysed slowly enough for the reaction to be monitored by u.v. or ^1H n.m.r. spectroscopy and the latter technique was used to determine the half-lives for hydrolysis at 35 °C under self-buffered conditions (the pK_a of the product was 5.56) [10] which were 3.6 h for (11a; R = Et) and 28.4 h for (11b; R = Et). The hydrolysis of (11b; R = Et) was also catalysed by phosphate buffer and the rates were measured at pH 7.2, *I* 0.5 mol dm^{-3}, and 25.0 °C by observing the appearance of the ylide product (10) at 370 nm. The results (Table 1) show a linear relationship between $k_{obs.}$ and $[H_2PO_4^-]$.

TABLE 1

Rate of hydrolysis of (11b; R = Et) in phosphate buffer (pH 7.2, *I* = 0.5 mol dm^{-3} and 25.0 °C)

$10^2[H_2PO_4^-]$/mol^{-1}	5.26	4.21	3.15	2.10	1.05	0.263
$10^5 k_{obs.}$/s^{-1}	1.14	0.962	0.778	0.589	0.405	0.265

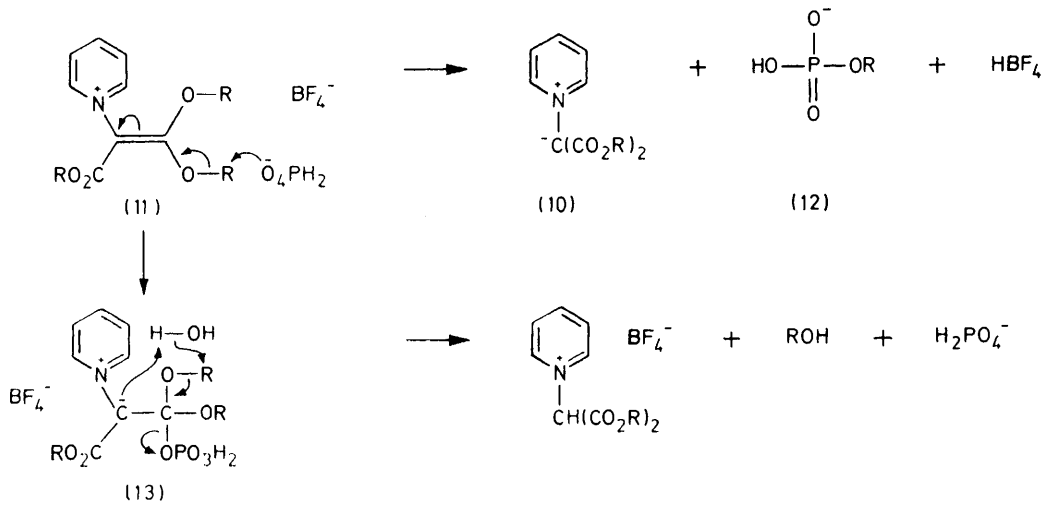
From the linear regression [equation (1)] and the expression for $k_{obs.}$ [equation (2)] assuming there is no dealkylation by water, one may derive the rate coefficients for catalysis by buffer, k_b = 1.76 l mol^{-1} s^{-1} and for

$$k_{obs.} = 1.76 \times 10^{-4}\,[H_2PO_4^-] + 2.22 \times 10^{-6} \quad (1)$$

$$k_{obs.} = k_b[H_2PO_4^-] + k_{OH^-}[OH^-] \quad (2)$$

dealkylation by OH^-, k_{OH^-} = 14.0 l mol^{-1} s^{-1}. It is not known whether the phosphate ion dealkylates (11) to form the monoester (12) or whether it merely acts as a nucleophilic catalyst *via* [(13)] as suggested in Scheme 4. In view of the results reported in the next section, however, the latter seems the more likely.

(2) *The Reaction of 'Onium Keten Acetals with Organophosphorus Acids and Organophosphorus Acid Anions.*—(a) *In non-aqueous media.* The reactions of the 'onium keten acetals (7) or (11) with phosphorus acids were carried out by mixing solutions of the appropriate keten acetal and the organophosphorus acid in chloroform or methylene chloride, and storing for up to twenty days at ambient temperature before analysing by ^{31}P n.m.r. In the case of the reaction between (7b) and *OO*-diethyl phosphorodithioic acid, an 80% yield of the *OO*-diethyl-*S*-methylphosphorodithioate was isolated from the reaction mixture by fractional distillation. In all other cases the phosphorus esters were identified by ^1H and ^{31}P n.m.r. Reactions of the 'onium keten acetals with phosphorus acid anions were carried out in methanol, dimethyl sulphoxide, or a mixture of solvents. Again



SCHEME 4

the products were analysed by ^{31}P n.m.r. and the results from both sets of experiments are summarised in Table 2. It is immediately obvious that, as observed with alkylketen acetals,[1-3] the phosphorodithioic acids give excellent yields of the corresponding esters with both types of 'onium keten acetal. With the phosphonic acids, however, the yields of esters from the 'onium keten acetals were very much lower (3—10%) than with diethyl methylketen acetal (80%). This suggests a different mechanism for the 'onium keten acetals, and (70%) and (11a) (100%), whereas only low yields (7—13%) are observed with sodium ethyl methylphosphonate.* Obviously the more nucleophilic dithioate anion would be the more reactive under these circumstances. The co-products in these cases are of course the ylides (8) and (10). Table 2 shows that alkylketen acetals are totally unreactive towards phosphorus acid anions, as would be expected from a mechanism dependent upon protonation of the substrate.

(b) *In aqueous media.* These experiments were carried

TABLE 2

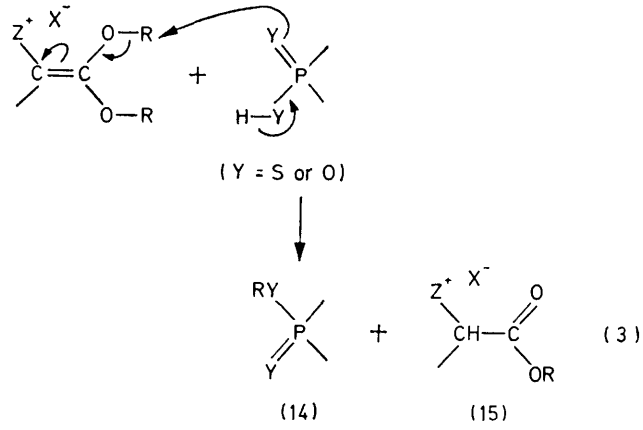
Reactions of keten acetals with phosphorus acids and phosphorus acid anions in non-aqueous media *

Keten Acetal	P-acid/salt	Solvent	Reaction conditions	P-ester	Yield (%)
(7a)	$(EtO)MePS_2^-$ Na^+	MeOH–MeCN (5 : 2)	20 °C, 190h	(EtO)MeP(S)SMe	75 ± 2
(7a)	$(EtO)MePO_2^-$ Na^+	MeOH–CH_2Cl_2–MeCN (11 : 2 : 2)	20 °C, 500h	(EtO)MeP(O)OMe	7 ± 2
(11a; R = Et)	$(EtO)MePS_2^-$ Na^+	DMSO	20 °C, 96h	(EtO)MeP(S)SEt	100 ± 2
(11a; R = Et)	$(EtO)MePO_2^-$ Na^+	MeOH–DMSO (1 : 4)	20 °C, 96h	(EtO)MeP(O)OEt	13 ± 2
(11a; R = Et)	$(EtO)MePO_2^-$ Na^+	MeOH–DMSO (1 : 4)	20 °C, 96h ratio 2 : 1	(EtO)MeP(O)OEt	24 ± 5
$CNCH=C(OMe)_2$	$(EtO)MePS_2^-$ Na^+	MeOH	20 °C, 500h	(EtO)MeP(S)SMe	0
$CNCH=C(OMe)_2$	$(EtO)MePO_2^-$ Na^+	MeOH	20 °C, 500h	(EtO)MeP(O)OMe	0
(7b)	$(EtO)_2PSSH$	$CHCl_3$	20 °C, 48h	$(EtO)_2P(S)SMe$	98 ± 2
(7b)	(EtO)MePSSH	$CHCl_3$	20 °C, 48h	(EtO)MeP(S)SMe	98 ± 2
(7b)	(EtO)MePOOH	$CHCl_3$	20 °C, 48h ratio 1 : 2	(EtO)MeP(O)OMe	<3
(11a; R = Et)	(EtO)MePSSH	CH_2Cl_2	35 °C, 96h	(EtO)MeP(S)SEt	98 ± 2
(11a; R = Et)	(EtO)MePOOH	CH_2Cl_2	35 °C, 96h	(EtO)MeP(O)OEt	10 ± 2
(11b; R = Et)	$(n\text{-}C_{16}H_{33}O)MePOOH$	$CHCl_3$	20 °C, 24h	$(n\text{-}C_{16}H_{33}O)MeP(O)OEt$	30 ± 4
$MeCH=C(OEt)_2$	$(EtO)_2PSSH$	C_6H_6	78 °C, 2h	$(EtO)_2P(S)SEt$	86[1,2]
$MeCH=C(OEt)_2$	(EtO)EtPOOH	C_6H_6	78 °C, 2h	(EtO)EtP(O)OEt	80[1,2]

* Molar ratio of reactants, 1 : 1 unless stated otherwise.

whereas the alkylketen acetals are known to react with organophosphorus acids in aprotic media by a fast reversible protonation, followed by rate-limiting attack of the acid anion on the protonated substrate,[2,3] we suggest that the 'onium keten acetals react by nucleophilic attack on an alkyl group (R) of the acetal [equation (3)] to generate the ester (14) and a salt (15). This proposal receives support from the observation that phosphonodithionate anion in non-aqueous media gives high yields of *O*-ethyl *S*-alkyl methylphosphonodithioate with (7a) out in water or mixtures of water with acetonitrile or tetrahydrofuran by adding a solution of the keten acetal to a solution of the sodium salt of the appropriate phosphorus acid in a 1 : 1 molar ratio at a pH of *ca.* 7.2. The results are summarised in Table 3 and it is again evident that the dithiophosphonate anions alkylate much more readily than the phosphonate anions. This serves to

* It should be noted however, that introduction of a long alkyl chain ($C_{16}H_{33}$) onto the phosphonic acid improves the yield of ester to *ca.* 30%, presumably due to a micellar effect.



reinforce the hypothesis that the 'onium keten acetals behave as conventional alkylating agents in reactions with various nucleophiles. Once again the alkyl or arylketen acetals do not react without acid catalysis, and there is further evidence for a micellar effect with hexadecylphosphonate anion.

dithiophosphonate anion very efficiently but is quite unreactive towards simple phosphonates. With hexadecyl methylphosphonate however, the extent of alkylation is the same (12%) as in aqueous medium and this reinforces the suggestion of reaction within the relatively aprotic environment of micelles for these particular acid anions. As expected, the conventional keten acetals gave no alkylation.

(d) *Reaction under phase-transfer conditions.* Hexadecyltrimethylammonium bromide was generally used as the phase-transfer catalyst for transporting the phosphorus acid anions from water to methylene chloride solutions of the keten acetals and the results are shown in Table 5. No experiments were undertaken with the hexadecyl methylphosphonate anion but only the phosphonodithioate reacted with the 'onium keten acetals to form esters. The conventional keten acetals as expected, were unreactive under these conditions.

In general, therefore, 'onium keten acetals react with nucleophiles by a different mechanism to keten acetals, *i.e.* by nucleophilic attack on acetal carbon. In this

TABLE 3

Reactions of keten acetals with phosphorus acid anions in aqueous media at pH 7.2 and molar ratio 1 : 1

Keten acetal	P-salt	Solvent	Reaction conditions	P-ester	Yield (%)
(7a)	$(EtO)MePS_2^-$ Na^+	H_2O–MeCN (2 : 1)	38 °C, 600h	(EtO)MeP(S)SMe	84 ± 2
(7a)	$(EtO)MePO_2^-$ Na^+	H_2O–MeCN (1 : 1)	45 °C, 240h +20 °C, 400h	(EtO)MeP(O)OMe	6 ± 2 [a]
(11b; R = Et)	$(EtO)MePS_2^-$ Na^+	H_2O	25 °C, 18h	(EtO)MeP(S)SEt	30 ± 1 [b]
(11b; R = Et)	$(EtO)MePS_2^-$ Na^+	H_2O	25 °C, 45h	(EtO)MeP(S)SEt	42 ± 1 [b]
(11b; R = Et)	$(EtO)MePO_2^-$ Na^+	H_2O	25 °C, 45h	(EtO)MeP(O)OEt	0 [b]
(11b; R = Et)	$(n\text{-}C_{16}H_{33}O)MePO_2^-$ Na^+	H_2O–THF (1 : 1)	20 °C, 48h	$(n\text{-}C_{16}H_{33}O)$MeP(O)OEt	12 ± 2
(11b; R = Et)	$(n\text{-}C_{16}H_{33}O)MePO_2^-$ Na^+	H_2O–THF (1 : 1)	20 °C, 430h	$(n\text{-}C_{16}H_{33}O)$MeP(O)OEt	32 ± 2
$CNCH{=}C(OMe)_2$	$(EtO)MePS_2^-$ NH_4^+	H_2O–MeCN (4 : 1)	31.4 °C, 24h	(EtO)MeP(S)SMe	0 [c]
$CNCH{=}C(OMe)_2$	$(EtO)MePO_2^-$ NH_4^+	H_2O–MeCN (1 : 1)	31.4 °C, 24h	(EtO)MeP(O)OMe	0 [c]

[a] 95% (7a) recovered. [b] KH_2PO_4–NaOH buffered. [c] For comparison purposes, none of the four keten acetals used in these experiments [*i.e.* $CNCH{=}C(OMe)_2$, $PhCH{=}C(OMe)_2$, $CH_2{=}C(OEt)_2$, and $MeCH{=}C(OEt)_2$] gave *any* phosphorus ester under these aqueous conditions.

TABLE 4

Reactions of keten acetals with phosphorus acid anions under emulsion conditions

Keten acetal	P-salt	Molar ratio	Initial pH	Medium	Surfactant % w/v	Reaction conditions	P-ester	Yield (%)
(11a; R = Et)	$(EtO)MePS_2^-$ Na^+	1 : 1	8.9	H_2O–CH_2Cl_2 (1 : 1)	2% Tween 20–cetyl alcohol (1 : 1)	20 °C, 48h	(EtO)MeP(S)SEt	99 ± 5
(11a; R = Et)	$(EtO)MePO_2^-$ Na^+	0.9 : 1	10.0	H_2O–CH_2Cl_2 (1 : 1)	2% Tween 20–cetyl acohol (1 : 1)	20 °C, 96h	(EtO)MeP(O)OEt	0
(11b; R = Et)	$(n\text{-}C_{16}H_{33}O)MePO_2^-$ Na^+	1 : 1	7.0	H_2O–CH_2Cl_2 (1 : 1)	None	20 °C, 48h	$(n\text{-}C_{16}H_{33}O)$MeP(O)OEt	12 ± 2
$CNCH{=}C(OMe)_2$	$(EtO)MePS_2^-$ NH_4^+	1 : 1	8.5	H_2O–C_6H_6 (4 : 1)	1% Tween 20	20 °C, 24h	(EtO)MeP(S)SMe	0
$CNCH{=}C(OMe)_2$	$(EtO)MePO_2^-$ NH_4^+	0.7 : 1	8.8	H_2O–C_6H_6 (4 : 1)	1% Tween 20	20 °C, 24h	(EtO)MeP(O)OMe	0

(c) *Reaction under emulsion conditions.* The salts of organophosphorus acids were dissolved in the water phase and emulsions made with either benzene or methylene chloride solutions of the keten acetals. After stirring for 24 h at ambient temperature, samples of the emulsions were dissolved in acetone and the products were analysed by ^{31}P n.m.r. The results (Table 4) reveal that the pyridinium keten acetal is capable of alkylating respect phosphoro- and phosphono-dithioates are much more effective nucleophiles than phosphonates, although there appears to be a micellar effect with long-chain alkyl (*e.g. O*-hexadecyl) phosphonates which enhances alkylation. There seems to be little prospect, however, of the 'onium keten acetals being useful as alkylating agents for simple phosphonate anions. On the other hand, the 'onium keten acetals may be useful for the

TABLE 5

Reactions of keten acetals with phosphorus acid anions under phase-transfer conditions

Keten acetal	P-salt	Molar ratio	Initial pH	Catalyst	Reaction conditions	P-ester	Yield (%)
(7a)	$(EtO)MePS_2^-$ Na^+	1 : 1	6.5	$C_{16}H_{33}\overset{+}{N}Me_3$ Br^-	20 °C, 100h	(EtO)MeP(S)SMe	96 ± 5
(7a)	$(EtO)MePO_2^-$ Na^+	1 : 1	6.5	$C_{16}H_{33}\overset{+}{N}Me_3$ Br^-	20 °C, 100h	(EtO)MeP(O)OMe	0
(11a; R = Et)	$(EtO)MePS_2^-$ Na^+	1 : 1	8.9	$C_{16}H_{33}\overset{+}{N}Me_3$ Br^-	20 °C, 75h	(EtO)MeP(S)SEt	94 ± 3
(11a; R = Et)	$(EtO)MePO_2^-$ Na^+	1 : 1	10.3	$C_{16}H_{33}\overset{+}{N}Me_3$ Br^-	20 °C, 120h	(EtO)MeP(O)OMe	0
$CNCH{=}C(OMe)_2$	$(EtO)MePS_2^-$ NH_4^+	1 : 1 *	5.2	$(EtO)MePS_2^-$ $^+NH_3C_{12}H_{25}$	20 °C, 40h	(EtO)MeP(S)SMe	0
$CNCH{=}C(OMe)_2$	$(EtO)MePO_2^-$ NH_4^+	1 : 1 *	5.2	$(EtO)MePO_2^-$ $^+NH_3C_{12}H_{25}$	20 °C, 40h	(EtO)MeP(O)OMe	0

* Includes the concentration of the anion from the catalyst.

alkylation of a range of ' soft ' nucleophiles (*e.g.* phenolate ion, amines, or thiocarboxylate ions) under aqueous conditions which could be useful for analytical purposes, *e.g.* by g.l.c.

EXPERIMENTAL

^1H N.m.r. spectra were recorded using either a 60 MHz Perkin-Elmer R12 B or a Bruker HFX 90 spectrometer with $SiMe_4$ as internal standard. The ^{31}P n.m.r. spectra were obtained at 36.4 MHz (HFX 90) with H_3PO_4 as external standard; downfield shifts are positive. Ultraviolet spectra and kinetic data were recorded using a Pye-Unicam SP 1700 spectrophotometer fitted with an AR 25 recorder and a thermostatted cell-housing operating at 25.0 ± 0.1 °C. Melting points are uncorrected and microanalyses were carried out by the microanalytical laboratory, University College, London. The emulsions were prepared using a Q.P. Laboratory Emulsifier (Ormerod Engineers Ltd., Rochdale).

Dialkyl cyanoketen acetals were prepared by established methods.[11,12]

2,2-Dimethoxy-1-(p-methoxyphenyl)vinyltriphenylphosphonium Fluorosulphonate (7b).—A solution of 4-methoxybenzyl bromide [13] (18.4 g, 0.091 mol) in benzene (20 ml) was added dropwise to a vigorously stirred solution of triphenylphosphine (24.0 g, 0.091 mol) in the minimum amount of dry benzene (*ca.* 100 ml) An exothermic reaction ensued and a white precipitate appeared. The mixture was stirred at ambient temperature for 24 h and the product was then filtered off, washed with benzene (3 × 50 ml), and dried under vacuum to give 42.4 g (100%) of 4-methoxybenzyltriphenylphosphonium bromide, m.p. 234—236 °C (lit.,[14] m.p. 235 °C); δ($CDCl_3$) 6.48—7.88 (19 H, m, Ar-H), 5.23 (2 H, d, ^2J_P 14.0 Hz, $CH_2C_6H_4OMe$), and 3.65 (3 H, s, OMe).

The 4-methoxybenzyltriphenylphosphonium bromide (41.7 g, 0.09 mol) was suspended in dry benzene (100 ml) and a solution of n-butyl-lithium (5.77 g, 0.09 mol) in n-hexane was added with vigorous stirring. After 1 h the deep red solution was filtered and a solution of methyl chloroformate (8.46 g, 0.09 mol) in dry benzene (20 ml) was added to the filtrate. A yellow suspension was produced and after stirring for 1 h at ambient temperature the mixture was filtered (to remove unwanted phosphonium salt) and methoxycarbonyl-4-methoxyphenylmethylenetriphenylphosphorane was precipitated from the filtrate by addition of light petroleum (b.p. 40—60 °C). The crude product was recrystallised from ethyl acetate–light petroleum to give 13.1 g (66%) of the pure *ylide* as colourless needles, m.p. 206—207 °C, (Found: C, 75.9; H, 5.8; P, 7.1. $C_{28}H_{25}O_3P$ requires C, 76.4; H, 5.7; P, 7.0%); δ_H ($CDCl_3$) 6.48—7.90 (19 H, m, Ar-H), 3.48 (3 H, s, CO_2Me), and 3.40 (3 H, s, OMe); δ_P ($CDCl_3$) 22.7.

A solution of the ylide (8.81 g, 0.02 mol) in CH_2Cl_2 (50 ml) was added dropwise to an ice-cold solution of methyl fluorosulphonate (2.28 g, 0.02 mol) in dry (from P_2O_5) CH_2Cl_2 (100 ml) under N_2. After 15 min stirring at ambient temperature, the solvent was removed under vacuum and the residual red-brown oil was triturated with light petroleum to give a buff solid. The crude material was recrystallised from 50% aqueous acetonitrile to give 7.80 g (70.3%) of the *title compound* (7b) as colourless plates, m.p. 185.5—187 °C (Found: C, 62.8; H, 5.1; P, 5.6. $C_{29}H_{28}FO_6PS$ requires C, 63.2; H, 5.1; P, 5.6%); δ_H ($CDCl_3$) 7.25—7.78 (15 H, m, PPh_3), 6.92 (2 H, dd, ^3J_H 8.7, ^3J_P 2.0 Hz, *o*-H of C_6H_4OMe), 6.64 (2 H, d, ^3J_H 8.7 Hz, *m*-H of C_6H_4OMe), 3.72 [3 H, s, (*E*)-OMe], 3.68 [3 H, s, (*Z*)-OMe], and 3.19 (3 H, s, *p*-OMe); δ_P ($CDCl_3$) 24.3.

2,2-Dimethoxy-1-phenylvinyltriphenylphosphonium Fluorosulphonate (7a).—This was prepared by an analogous route in an overall yield of 50% from triphenylphosphine, and was obtained as colourless cubic crystals from 50% aqueous acetonitrile, m.p. 200.5—201.5 °C (Found: C, 64.1; H, 5.2; P, 6.1. $C_{28}H_{26}FO_5PS$ requires C, 64.1; H, 5.0; P, 5.9%); δ_H ($CDCl_3$) 7.33—7.92 (15 H, m, PPh_3), 6.90—7.25 (5 H, m, C–Ph), 3.67 [3 H, s, (*E*)-OMe], and 3.22 [3 H, s, (*Z*)-OMe]; δ_P ($CDCl_3$) 24.5.

N-(1-Ethoxycarbonyl-2,2-diethoxyvinyl)pyridinium fluorosulphonate and Tetrafluoroborate (11a,b).—Pyridine (3.6 g, 0.044 mol) was added dropwise to a solution of diethyl bromomalonate (10.6 g, 0.044 mol) in dry acetone (75 ml) and the mixture was stirred for 18 h at ambient temperature. Rapid cooling (solid CO_2 – acetone) precipitated a buff-coloured solid which was filtered, washed with dry ether, and dried under vacuum to give 12.5 g (89%) of *N*-bis(ethoxycarbonyl)methylpyridinium bromide, m.p. 93—94 °C (lit.,[15] m.p. 70—71 °C); δ_H ($CDCl_3$) 9.73 (2 H, m, α-H of pyridinium ring), 8.97 (1 H, m, γ-H), 8.35 (2 H, m, β-H), 8.00 (1 H, s, $\overset{+}{N}CH$), 4.41 (4 H, q, *J* 7.0 Hz, $CO_2CH_2CH_3$), and 1.40 (6 H, t, *J* 7.0 Hz, $CO_2CH_2CH_3$).

A solution of potassium carbonate (13.8 g, 0.1 mol) in water (50 ml) was added to a solution of *N*-bis(ethoxycarbonyl)methylpyridinium bromide (6.3 g, 0.02 mol) in water (50 ml) and the resultant yellow-orange solution was extracted with chloroform (5 × 100 ml). The chloroform extracts were dried over sodium sulphate, the solvent removed under vacuum, and the yellow solid recrystallised from acetone to give 4.6 g (97%) of bis(ethoxycarbonyl)-methylene-*N*-pyridinium ylide (10; R = Et) as yellow needles, m.p. 176.5—177.5° (lit.,[15] m.p. 170—171 °C); δ_H

($CDCl_3$), 8.53 (2 H, m, α-H), 8.03 (1 H, m, γ-H), 7.60 (2 H, m, β-H), 4.08 (4 H, q, *J* 7.0 Hz, $CO_2CH_2CH_3$), and 1.20 (6 H, t, *J* 7.0 Hz, $CO_2CH_2CH_3$).

The ylide (10; R = Et) (10.2 g, 0.043 mol) was dried under vacuum, stored under N_2, methylene chloride (150 ml) was distilled from P_2O_5 onto the ylide, and freshly distilled ethyl fluorosulphonate (6.1 g, 0.047 mol) added. The flask was sealed under N_2 and stored at ambient temperature. All the suspended ylide dissolved during 2 h and the mixture, which was originally orange, became pale yellow. After 7 days the solvent was removed at 35 °C and the residual yellow syrup was triturated (×3) with dry dimethyl ether at −40 °C. The resultant white crystalline solid was dried under vacuum (0.01 Torr) at 25 °C for 4 h to give 15.7 g (99%) of *1-ethoxycarbonyl-2,2-diethoxyvinyl-N-pyridinium fluorosulphonate* (11a) as white needles, m.p. 83—86 °C. Attempts to recrystallise the product resulted in extensive hydrolysis and satisfactory analyses were not obtained, apparently due to partial hydrolysis; δ_H ($CDCl_3$) 8.85 (2 H, d, *J* 5.6 Hz, α-H), 8.63 (1 H, m, γ-H), 8.16 (2 H, m, β-H), 4.71 [2 H, q, *J* 7.0 Hz, (*E*)-OCH_2CH_3], 4.27 (2 H, q, *J* 7.0 Hz, $CO_2CH_2CH_3$), 4.20 [2 H, q, *J* 7.0 Hz, (*Z*)-OCH_2CH_3], 1.54 [3 H, t, *J* 7.0 Hz, (*E*)-OCH_2CH_3], 1.20 (3 H, t, *J* 7.0 Hz, $CO_2CH_2CH_3$), and 1.16 [3 H, t, *J* 7.0 Hz, (*Z*)-OCH_2CH_3].

The ylide (10; R = Et) (6.4 g, 0.027mol) was added to a solution of triethyloxonium tetrafluoroborate (4.7 g, 0.025 mol) in dry CH_2Cl_2 (175 ml) and the solution was stirred at ambient temperature for 7 days. The solvent was then removed under vacuum (0.01 Torr) at 45 °C and the pale orange syrup was triturated with dry diethyl ether in a dry box. The yellow solid which precipitated was filtered off, washed with ether, and dried under vacuum (0.01 Torr, 25 °C). An aqueous solution (*ca.* 0.5M) of the crude product when cooled to 4 °C gave 4.7 g (54%) of N-(*1-ethoxycarbonyl-2,2-diethoxyvinyl*)*pyridinium tetrafluoroborate* (11b)as colourless needles, m.p. 91.5—92.5 °C (Found: C, 47.0; H, 5.8; N, 3.9. $C_{12}H_{20}BF_4NO_2$ requires C, 47.6; H, 5.7; N, 4.0%); $\nu_{max.}$ (KBr disc) 1 705 C=O) and 1 630 cm^{-1} (C=C); $\lambda_{max.}$ (H_2O) 249 (log ε 4.23) and 300 nm (shoulder); δ_H ($CDCl_3$) 8.77 (2 H, dd, *J* 4.5, 1.5 Hz, α-H), 8.61 (1 H, m, γ-H), 8.12 (2 H, m, β-H), 4.70 [2 H, q, *J* 7.0 Hz, (*E*)-OCH_2CH_3], 4.27 (2 H, q, *J* 7.0 Hz, $CO_2CH_2CH_3$), 4.19 [2 H, q, *J* 7.0 Hz, (*Z*)-OCH_2CH_3], 1.53 [3 H, t, *J* 7.0 Hz, (*E*)-OCH_2CH_3], 1.20 (3 H, t, *J* 7.0 Hz, $CO_2CH_2CH_3$), and 1.15 [3 H, t, *J* 7.0 Hz (*Z*)-OCH_2CH_3].

Reactions of Keten Acetals with Organophosphorus Acids and Acid anions.—Typical results are reported below.

(1) *With acids in aprotic media.* A solution of *O*-ethyl methylphosphonodithioic acid (2 ml, 0.5M) in $CHCl_3$ was added to a $CDCl_3$ solution of (7a) (2 ml, 0.5M) and the mixture was stirred at ambient temperature for two days before analysis by ^{31}P n.m.r. Calibration curves were set up for each phosphorus ester produced using authentic samples of the esters and either triethyl phosphate or *O*-ethyl *O*-methyl methylphosphonate as standards and constructing graphs of molar ratios *vs.* peak height ratios.

(2) *With acid anions in non-aqueous media.* A solution of (11a; R = Et) (0.73 g, 2 × 10^{-3} mol) in dimethyl sulphoxide (5 ml) was added to a solution of sodium *O*-ethyl methylphosphonate (0.29 g, 2 × 10^{-3} mol) in methanol–dimethyl sulphoxide (2 : 3) (5 ml) and the mixture was sealed in a Reacti Vial ® and stored at a temperature between 25 and 40 °C for 4 days before analysis by ^{31}P n.m.r.

(3) *With acid anions in aqueous media at* pH 7.2. A solution of cyanoketen dimethyl acetal (0.34 g, 3 × 10^{-3} mol) in acetonitrile (2 ml) was added rapidly to a solution of ammonium *O*-ethyl methylphosphonothionothiolate (0.52 g, 3 × 10^{-3} mol) in phosphate buffer (8 ml) at pH 7.2 and was maintained at 31.4 °C for 24 h before analysis by ^{31}P n.m.r. (examination by u.v. spectroscopy revealed that the keten acetal had disappeared completely after 8 h).

(4) *With acid anions under emulsion conditions.* A solution of cyanoketen dimethyl acetal (0.85 g, 7.5 × 10^{-3} mol) in dry benzene (5 ml) was shaken vigorously with a solution of ammonium *O*-ethyl methylphosphonate (1.06 g, 7.5 × 10^{-3} mol) in water (20 ml, pH 8.8) for about 30 s before the mixture was emulsified by three passes through the emulsifier. The resultant emulsion, of mean droplet size *ca.* 1.5μm, was stirred magnetically at 20 °C in a sealed bottle for 24 h. A sample (1 ml) of the emulsion was withdrawn and diluted with acetone (2 ml) to give a homogeneous solution which was analysed by ^{31}P n.m.r.

(5) *With acid anions under phase-transfer conditions.* A solution of (11a, R = Et) (0.66 g, 1.8 × 10^{-3} mol) in CH_2Cl_2 (10 ml) was added over 15 s to a rapidly stirred solution of sodium *O*-ethyl methylphosphonothionothiolate (0.71 g, 4 × 10^{-3} mol) in water (10 ml, pH 8.9) containing cetyltrimethylammonium bromide (0.15 g, 4 × 10^{-3} mol) and the mixture was stirred magnetically at *ca.* 500 r.p.m. at 20 °C for three days in a sealed bottle. The mixture was then allowed to settle and 0.5 ml of each layer was carefully removed by pipette, diluted with methanol, and the homogeneous solutions were analysed by ^{31}P n.m.r.

[1/649 *Received*, 23*rd April*, 1981]

REFERENCES

[1] C. D. Hall, *J. Chem. Soc. B*, 1968, 708.
[2] P. G. Le Grâs, R. L. Dyer, P. J. Clifford and C. D. Hall, *J. Chem. Soc., Perkin Trans. 2*, 1973, 2046.
[3] (*a*) R. L. Dyer and C. D. Hall, *Chem. Ind. (London)*, 1973, 1109; (*b*) R. L. Dyer, P. G. Le Grâs, and C. D. Hall, *J. Chem. Soc., Perkin Trans. 2*, 1976, 1613.
[4] V. Gold and D. C. A. Waterman, *J. Chem. Soc. B*, 1968, 839, 849.
[5] (*a*) I. B. Wilson, S. Ginsberg and C. Quan, *Arch. Biochem. Biophys.*, 1958, **77**, 286; (*b*) F. Hobbiger and W. Sadler, *Nature (London)*, 1958, **182**, 1672.
[6] I. B. Wilson and E. K. Meislich, *J. Am. Chem. Soc.*, 1953, **75**, 4628.
[7] H-J. Bestmann, H. Schulz and E. Kranz, *Angew. Chem., Int. Ed. Engl.*, 1969, **8**, 216.
[8] H-J. Bestmann, R. W. Saalfrank and J. P. Snyder, *Chem. Ber.*, 1973, **106**, 2601.
[9] J. Emsley and C. D. Hall, 'The Chemistry of Phosphorus,' ch. 7, Harper and Row, London, 1976.
[10] O. Ya. Neilands and S. V. Kalnin, *J. Org. Chem. USSR, (Engl. Transl.)*, 1968, **4**, 132.
[11] S. M. McElvain and J. P. Schroeder, *J. Am. Chem. Soc.*, 1949, **71**, 40, 47.
[12] S. A. Glickman and A. C. Cope, *J. Am. Chem. Soc.*, 1945, **67**, 1017.
[13] A. Lapworth and J. B. Shoesmith, *J. Chem. Soc.*, 1922, 1391.
[14] H-J. Bestmann, E. Vilsmaier and G. Graf, *Liebigs Ann. Chem.*, 1967, **704**, 109.
[15] F. Kröhnke, *Chem. Ber.*, 1937, **70**. 543.