Tetrahedron. Vol 29, pp. 3741 to 3752. Pergamon Press 1973 Printed in Great Britain

5-MEMBERED CYCLIC ACYL PHOSPHATES
A NEW CLASS OF EXTREMELY REACTIVE PHOSPHORYLATING AGENTS

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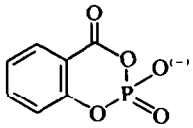
(*Received in the USA 2 April 1973; Received in the UK for publication 9 July 1973*)

Abstract—The reaction of phosgene with the oxyphosphorane made from biacetyl and trimethyl phosphite gives an α-(dimethylphosphato)-β-ketoacid chloride, which undergoes an intramolecular loss of methyl chloride under catalysis by $CuSO_4$, and yields the first reported 5-membered cyclic acyl phosphate. The acyl phosphate is attacked exclusively at phosphorus by water, alcohols and phenols, at an extraordinarily rapid rate. In contrast, tertiary amines attack only the Me carbon of the exocyclic OMe group of the acyl phosphate to give quaternary ammonium salts of 5-membered cyclic acyl phosphates. These cyclic mixed anhydrides of phosphoric acid are the most powerful phosphorylating agents for oxygen-containing nucleophiles known at present. The end-products of the phosphorylations are phosphotriesters, phosphodiesters, and phosphomonoesters, containing the easily removable acetoinyl group, $[(CH_3CO)(CH_3)CHO]P(O)(OR)(OR')$.

INTRODUCTION

The acyl phosphates, $RCO.O.P(O)(OH)_2$, have been investigated for many years,[1-5] and their significance in biochemistry has been recognized for quite some time.[2,3,6-9] Acetylphenyl phosphate,[10-14] $CH_3CO.O.P(O)(OC_6H_5)(OH)$, and the acyldialkyl phosphates[15-19] $RCO.O.P(O)(OR')_2$, have also received considerable attention, in particular in connection with their dual behavior as acylating and phosphorylating agents:[7,8,10,20-24]



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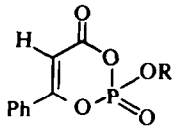

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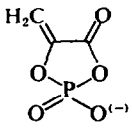

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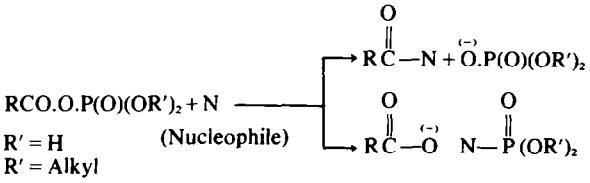
RESULTS

The α-(dialkylphosphato)-β-ketoacid chloride, **5**, was made, *via* the oxyphosphorane **4**, by significant



improvements of reactions already described.[29,30] Pyrolysis of the acid chloride, **5**, in the presence of catalytic amounts of $CuSO_4$ resulted in the rapid loss of methyl chloride and the formation of two diastereomeric methyl esters of the 5-membered cyclic acyl phosphate, **6A** and **6B** (abbreviated as methyl-CAP).

The mixture of isomers, **6A**+**6B**, was purified by distillation, and the isomers were separated by fractional crystallization. The interconversion between the isomers was effectively catalyzed by pyridine;

6-Membered cyclic acyl phosphates, **1** and **2**, have been studied by Bender[25] and by Marecek and Griffith.[26] The formation of a cyclic 5-membered acyl phosphate, **3**, as a reaction intermediate was postulated by Clark and Kirby,[27a] and has been given strong support by the investigations of Benkovic and Schray.[27b-d]

This paper describes the preparation and some reactions of the 5-membered cyclic acyl phosphate which was recently reported in a Preliminary Communication.[28]

Table 1. NMR data[a] on 5-membered cyclic acyl phosphates (CAP's) and related compounds

No.	Compound	$\delta^{31}P$	CH_3CO τ	CH_3C τ	CH_3C J_{HCCH}	CH_3OP τ	CH_3OP J_{HCOP}	Additional ^1H signals
5	2-(Dimethylphosphato)-2-methyl-3-oxobutanoyl Chloride	+3·0	7·62	8·10	none	6·15 6·10	11·0 11·5	none
6A	*cis*-Oxo/Acetyl Methyl-CAP[b]	−2·42	7·62	8·23	none	6·02	12·0	none
6B	*trans*-Oxo/Acetyl Methyl-CAP[b]	−2·66	7·66	8·13	none	6·02	12·0	none
14a	N-Methylpyridinium-CAP[c]	−2·26	7·65	8·36	none	none		$\tau = 5{\cdot}46$[d] ($N{-}CH_3$)
14b	N,γ-Dimethylpyridinium-CAP	—	7·63	8·38	none	none		$\tau = 5{\cdot}48$ ($N{-}CH_3$) and 7·32 ($\gamma{-}CH_3$)
14c	Tetramethylammonium-CAP	—	7·62	8·33	none	none		$\tau = 6{\cdot}85$ ($N{-}CH_3$)
8	2-(Methylphosphato)-2-methyl-3-oxobutanoic Acid[e]	—	7·66	8·18	none	6·19	11·5	
10	Methyl 2-(Dimethylphosphato)-2-methyl-3-oxobutanoate	—	7·68	8·20	none	6·20[f] 6·15	11·5 11·5	$\tau = 6{\cdot}20$ ($COOCH_3$)
12	2-(Dimethylphosphato)-2-methyl-3-oxobutanoic Acid	—	7·66	8·18	none	6·16[f] 6·10	12·0 12·0	$\tau \simeq -2{\cdot}05$ (COOH)
19A,	2-(Methylethylphosphato)-2-methyl-3-oxobutanoic Acid	—	7·66	8·21	none	6·18	11·8	$\tau = 8{\cdot}61$; J = 7·1; J = 1·3 $\tau = 5{\cdot}62$; J = 7·1; J = 9·0 CH_3CH_2OP $\tau = 6{\cdot}24$ ($COOCH_3$)
22A, R = Et	Methyl 2-(methylethylphosphato)-2-methyl-3-oxobutanoate	—	7·70	8·23	none	6·22	11·2	$\tau = 8{\cdot}65$; J = 7, J = 1 $\tau = 5{\cdot}80$; J = 7, J = 9·0 CH_3CH_2OP
22A, $R = C_6H_5CH_2$	2-(Methylbenzylphosphato)-2-methyl-3-oxobutanoic Acid	—	7·70	8·16	none	6·20	12·0	$\tau = 4{\cdot}67$; $J_{HP} = 8$ ($C_6H_5CH_2$) $\tau = 2{\cdot}57$ (C_6H_5) $\tau \simeq -0{\cdot}27$ (COOH)
19A, R = i-Pr	2-(Methylisopropylphosphato)-2-methyl-3-oxobutanoic Acid	—	7·63	8·19	none	6·18	11·8	$\tau = 8{\cdot}59$ $J_{HH} = 7{\cdot}2$ Hz ($CH_3{-}\underset{\displaystyle CH_3}{\overset{\displaystyle |}{CH}}{-}$
9	Methyl (1-methyl-2-oxopropyl) Phosphate	—	7·73	8·52	7·0	6·22	11·5	$\tau = 5{\cdot}25$; $J_{HCOP} = 8{\cdot}5$, $J_{HCCH} \simeq 7{\cdot}0$ (methine-H)
13	Dimethyl (1-methyl-2-oxopropyl) Phosphate	−0·4	7·76	8·52	7·0	6·20[f] 6·16	11·5 11·5	$\tau = 5{\cdot}21$; $J_{HCOP} = 8{\cdot}5$, $J_{HCCH} = 7{\cdot}0$ (methine-H)
20A; 21A; R = Et	Methylethyl (1-methyl-2-oxopropyl) Phosphate	−1·6	7·73	8·50	7·0	6·18	11·4	$\tau = 8{\cdot}61$ $J_{HH} = 7$ Hz (CH_3CH_2) $\tau = 5{\cdot}17$ $J_{HP} \simeq 7{\cdot}4$ Hz ($CH_3\underset{\displaystyle |}{C}H$)
		−1·6	7·73	8·50	7·0	6·17	11·4	$\tau = 5{\cdot}76$ $J_{HP} = 9$ $J_{HH} = 7{\cdot}4$ Hz (CH_3CH_2) $\tau = 8{\cdot}61$ $J_{HH} = 7$ Hz (CH_3CH_2) $\tau = 5{\cdot}17$ $J_{HP} = 7{\cdot}4$ Hz ($CH_3\underset{\displaystyle |}{C}H$)
20A; 21A; $R = C_6H_5CH_2$	Methylbenzyl (1-methyl-2-oxopropyl) Phosphate	—	7·82	8·60	6·9	6·23	11·4	$\tau = 5{\cdot}76$ $J_{HP} = 1{\cdot}8$ Hz $J_{HH} = 7{\cdot}4$ Hz (CH_3CH_2) $\tau = 2{\cdot}58$ (C_6H_5) $\tau = 4{\cdot}83$ $J_{HP} = 8{\cdot}5$ ($C_6H_5CH_2$)
		—	7·87	8·62	6·9	6·28	11·5	$\tau = 2{\cdot}58$ (C_6H_5) $\tau = 4{\cdot}89$ $J_{HP} = 9{\cdot}0$ ($C_6H_5CH_2$)

20A; 21A; R = i-Pr	Methylisopropyl (1-methyl-2-oxopropyl) Phosphate	+1·8 +3·6	7·72 7·72	8·53 8·53	6·9 6·9	6·18 6·20	11·3 11·3	$\tau = 8{\cdot}63$ $J_{HH} = 6{\cdot}3$ Hz (CH_3—CH(CH_3))
16a	N-Methylpyridinium (1-methyl-2-oxopropyl) Phosphate	—	7·89	8·77	7·0	none		$\tau = 5{\cdot}41$ (N—CH_3)
18a	N-Methylpyridinium methyl (1-methyl-2-oxopropyl) Phosphate	—	7·89	8·78	7·0	6·55	11·0	$\tau = 5{\cdot}47$ (N—CH_3) $\tau = 5{\cdot}54$; $J_{HCOP} = 8{\cdot}5$, $J_{HCCH} = 7{\cdot}0$ (methine-H)

[a] ^{31}P Chemical shifts in parts per million *vs* $H_3PO_4 = 0$, at 40·5 MHz, at 25°, in CH_2Cl_2 unless otherwise specified. ^1H shifts in ppm *vs* $(CH_3)_4Si = 10$ (τ values), at 60 MHz, at 25°, in $CDCl_3$ unless otherwise specified. Coupling constants J in Hz. The integrated intensities of the ^1H NMR signals were in agreement with the assigned structures.

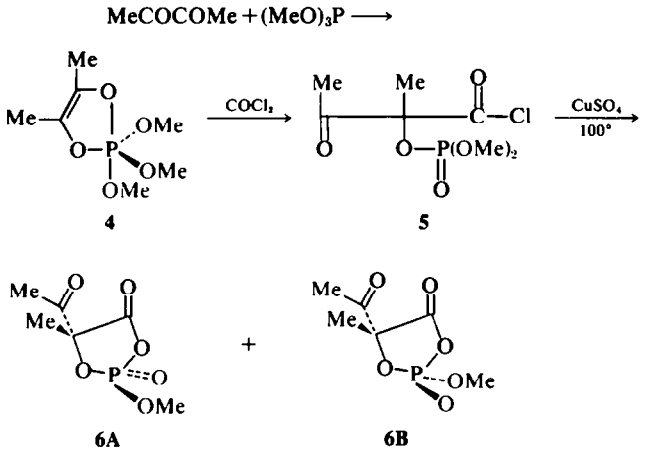
[b] Methyl-CAP = cyclic anhydride of 2-(methylphosphato)-2-methyl-3-oxobutanoic acid.

[c] N-Methylpyridinium salt of cyclic anhydride of 2-phosphato-2-methyl-3-oxobutanoic acid. Signals listed are in $CDCl_3$. Signals in benzene solution containing some pyridine: $\tau = 8{\cdot}33$, 7·62 and 5·45 ppm.

[d] Authentic N-methylpyridinium iodide had $\tau = 5{\cdot}46$ ppm in acetonitrile. The solution obtained by mixing acetonitrile solutions of N-methylpyridinium-CAP and N-methylpyridinium iodide had a singlet at $\tau = 5{\cdot}46$ ppm, in addition to singlets at $\tau = 8{\cdot}32$ and 7·58 ppm (CH_3C and CH_3CO of Py-CAP) (the acetonitrile signal was at $\tau = 7{\cdot}85$).

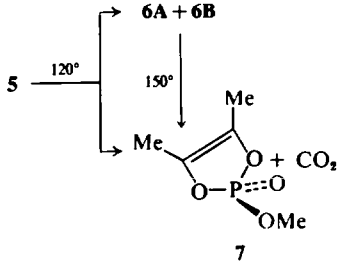
[e] Signals in dioxane-D_8.

[f] The two methoxy groups are magnetically non-equivalent, (as in **5**, Ref. 30).



the equilibrium mixture in $CDCl_3$ solution at 25° consisted of *ca* 70% (**6A**): 30% (**6B**). The structure and configuration of the methyl-CAP's, **6A**, **6B**, were based on the analytical and spectral data furnished in the Experimental and in Table 1. The acetyl group of the more stable isomer (**6A**) was less shielded, and its ring-Me group was more shielded, than the corresponding groups of the less stable isomer (**6B**), in the ^1H NMR spectra. For reasons given earlier,[31] this was taken as an indication that the acetyl group was adjacent to the phosphoryl oxygen, and the ring-Me was adjacent to the OMe group in **6A**. (The Me-CAP's will be designated as **6**, unless the stereochemistry at P becomes relevant.)

The pyrolysis of the acid chloride, **5**, in the absence of $CuSO_4$ required higher temperatures, was significantly slower, and produced the Me-CAP, **6**, and the known[32] methyl acetoinenediol cyclophosphate, **7**, in about equal amounts. Most of the enediol cyclophosphate, **7**, produced in the pyrolysis of **5** probably arose from some intermediate and not from Me-CAP, **6**, since the latter did not yield the cyclophosphate, **7**, at a significant rate under the pyrolysis conditions. The Me-CAP, **6**, however, also generated the cyclophosphate, although at higher temperatures. (The cyclophosphate **7** was a minor by-product (*ca* 5%) in the synthesis of the Me-CAP, **6**, by the $CuSO_4$-procedure.)



Me-CAP, **6**, reacted with water at an extraordinarily rapid rate, as shown in Table 2. The main

Table 2. Approximate rates of reaction[a] of the five-membered cyclic acyl phosphate (*cis*-Methyl-CAP, (**6A**) and of acetoinenediol cyclophosphate (**7**)

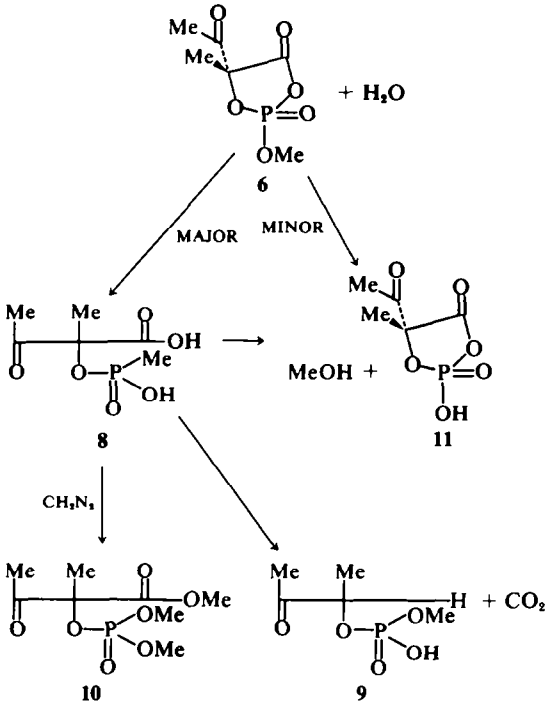
Reagent	Solvent	Me-CAP (**6**)	Enediol cyclophosphate (**7**)
H_2O	Dioxane, Dioxane-D_8	Complete reaction in < 15 sec	$t_{\frac{1}{2}} = 150$ sec
CH_3OH, C_2H_5OH, $C_6H_5CH_2OH$ $(CH_3)_2CHOH$	$CDCl_3$	Complete reaction in < 15 sec	—
$(CF_3)_2CHOH$		$t_{\frac{1}{2}} = 4$ days	
$(CH_3)_3COH$	$CDCl_3$	$t_{\frac{1}{2}} = 135$ sec	$t_{\frac{1}{2}} = ca.$ 8 days
C_6H_5OH	$CDCl_3$	$t_{\frac{1}{2}} = 160$ sec	—
$pCH_3OC_6H_5OH$		$t_{\frac{1}{2}} = 45$ sec	

[a]One molequivalent of water, the alcohol or phenol was added to a 0·1 M soln of crystalline *cis*-methyl-CAP (**6A**), or of the enediol cyclophosphate (**7**) in the solvent indicated, at 24°. The disappearance of **6A** and of **7** was followed by ^1H NMR spectrometry.

hydrolysis product was methyl phosphoacetoin, (9) formed by decarboxylation of the β-ketoacid **8**. Two minor hydrolysis products were methanol and the highly reactive acid-CAP, **11**, which could not be fully characterized. The acid-CAP, **11**, could have been produced from the Me-CAP, **6**, as discussed below; however, since carboxyl participation in related systems has been demonstrated,[27b-d] the formation of the acid-CAP, **11**, from the β-ketoacid **8**, is also possible.

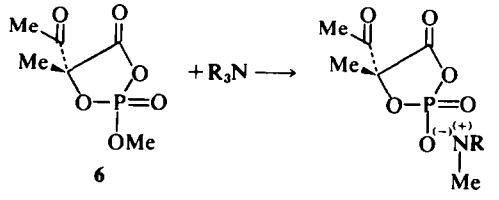
The decarboxylation of the β-ketoacid, **8**, was much slower than the hydrolysis of the Me-CAP, **6**, and the formation of the former, **8**, could be demonstrated by ^{1}H NMR spectrometry and by esterification to the phosphotriester-β-ketoester, **10**.

The hydrolysis of Me-CAP, **6**, was faster than that of the highly reactive enediol cyclophosphate,[32] **7**.



The phosphorylation of methanol by Me-CAP, **6**, occurred very rapidly in non-polar solvents, even in dilute solutions at 0°; see Table 2. The initial product was the phosphotriester-carboxylic acid, **12**, (Table 1), which underwent a relatively slow decarboxylation to dimethyl phosphoacetoin (**13**). The intermediate, **12**, could be esterified to the same neutral ester, **10**, previously obtained.

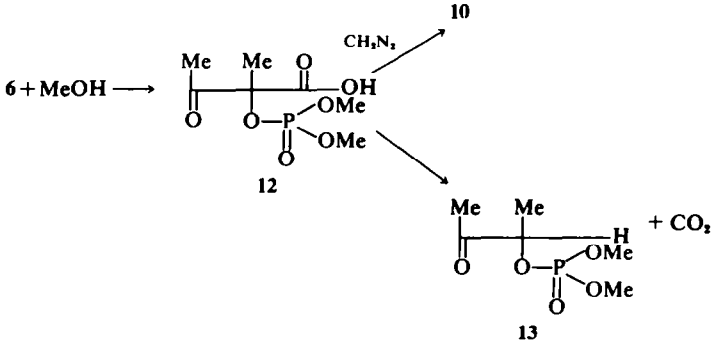
As mentioned above, catalytic amounts of pyridine caused the rapid stereomutation of pure *cis*-Me-CAP, **6A**. When stoichiometric amounts of pyridine were employed, the final product of the reaction was the N-methylpyridinium salt of a cyclic acyl phosphate anion, **14a**, (abbreviate as N-methylpyridinium-CAP). The structure of the CAP-salt, **14a**, was based on the NMR data given in Table 1, and in the regeneration of the original Me-CAP, **6**, upon treatment of **14a** with trimethyloxonium tetrafluoroborate. Methyl-CAP, **6**, also methylated other tertiary amines, *e.g.*, γ-picoline and trimethyl amine, to give the salts, **14b** and **14c**, respectively.

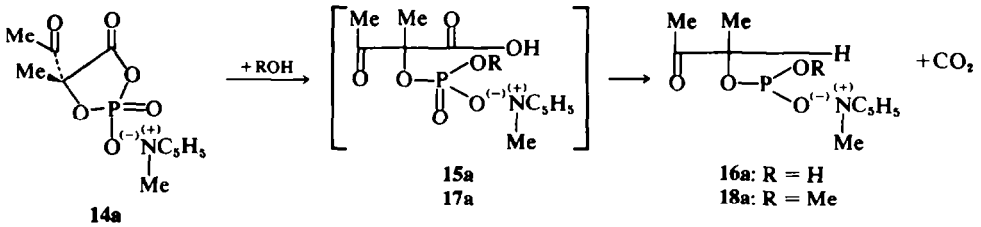


$R_3N = C_5H_5N$; **14a**
$R_3N = \gamma.Me.C_5H_4N$; **14b**
$R_3N = Me_3N$; **14c**

N-Methylpyridinium-CAP, **14a**, was also an extraordinarily powerful phosphorylating agent; its reaction with one molequivalent of water or methanol led, within minutes, to N-methylpyridinium phosphoacetoin (**16a**), and N-methylpyridinium methylphosphoacetoin (**18a**), respectively, in methylene chloride at 25°. Pyridine was an excellent solvent for carrying out the phosphorylation of alcohols by N-methylpyridinium-CAP, **14a**.

The phosphorylation of a series of 1°, 2° and 3° alcohols with *cis*-Me-CAP, **6A**, was investigated,

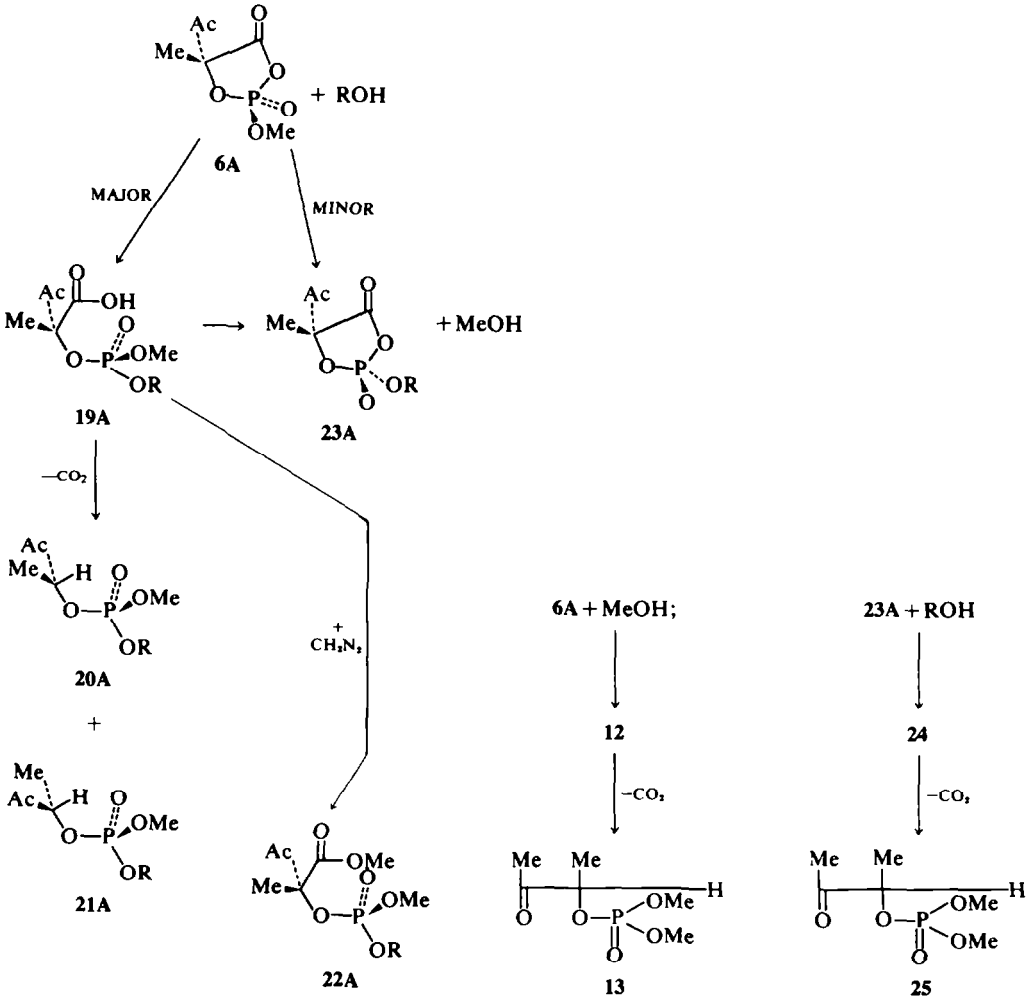




14a 15a 17a 16a: R = H 18a: R = Me

and the results are shown in Tables 1 and 2. The reaction with t-butyl alcohol was significantly slower than those with 1° and 2° alcohols. It was not possible, however, to establish any distinction between the very fast reaction rates of 1° *vs* 2° alcohols. Phenol reacted at approximately the same rate as t-butyl alcohol. The main product of the reaction of *cis*-Me-CAP, **6A**, with a given alcohol, ROH, was the α-(methylalkylphosphato)-β-ketoacid, **19A**, which was formed with complete stereospecificity (probably with inversion of the phosphorus chirality, as discussed below). Decarboxylation afforded the two diastereomeric methylalkyl phosphoacetoins, **20A** + **21A**. This lack of stereospecificity is not surprising since an enol⇌keto equilibration is presumably involved. The intermediate ketoacid, **19A**, could be "trapped" as its methyl ester, **22A**.

Two minor by-products were obtained in the reactions of *cis*-Me-CAP, **6A**, with a given alcohol, ROH, other than methanol. One of these by-products was dimethyl phosphoacetoin, **13**, in all



6A 19A 23A 20A 21A 22A 13 25

cases. The second by-product was the dialkyl phosphoacetoin, **25**. Dimethyl phosphoacetoin, **13**, stemmed from the reaction of the original Me-CAP, **6A**, with the methanol formed in the transesterification to the alkyl-CAP, **23A**. The dialkyl phosphoacetoin, **25**, arose from the reaction of the alkyl-CAP, **23A**, with the alcohol, ROH. In some experiments, the transient formation of the alkyl-CAP, **23A**, could be verified by direct observation of its ^{31}P NMR signal.

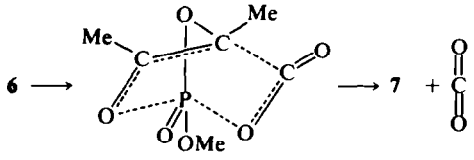
The transesterification of the Me-CAP, **6A**, to the alkyl-CAP, **23A**, is analogous to the hydrolysis with ring-retention, **6**→**11**. Again, the alkyl-CAP, **23A**, may have resulted from the methyl-CAP, **6A**, or from the β-ketoacid intermediate, **19A**, by carboxyl-participation.[27b-d]

DISCUSSION OF RESULTS

The experimental and theoretical background that now exists on the structure and the stereochemistry of the stable oxyphosphoranes,[29, 31, 34, 35] provides an adequate interpretation for the observations reported in this paper. On the assumption that metastable oxyphosphoranes, or P(5) compounds, are intermediates in nucleophilic displacements of four-coordinate phosphorus compounds, P(4), one can develop a series of rules that allow a consistent interpretation,[36] which extends and significantly modifies the previous views,[29c, 31c, d, 37-40] of the mechanisms of these reactions. An integral part of the "oxyphosphorane concept[36]" is the turnstile rotation mechanism[34, 35] or TR, for permutational isomerization of P(5).

The formation of Me-CAP, **6**, from the acid chloride, **5**, is interpreted according to Scheme 1. The formation of the enediol cyclophosphate, **7**, is assumed to involve several P(5) intermediates (the possible TR-processes have been omitted). The $CuSO_4$ prevents the formation of the enediol cyclophosphate, **7**, by facilitating the displacement of $Cl^{(-)}$, and by complexing with it, thus preventing the formation of an intermediate P(5) with a P—Cl bond.

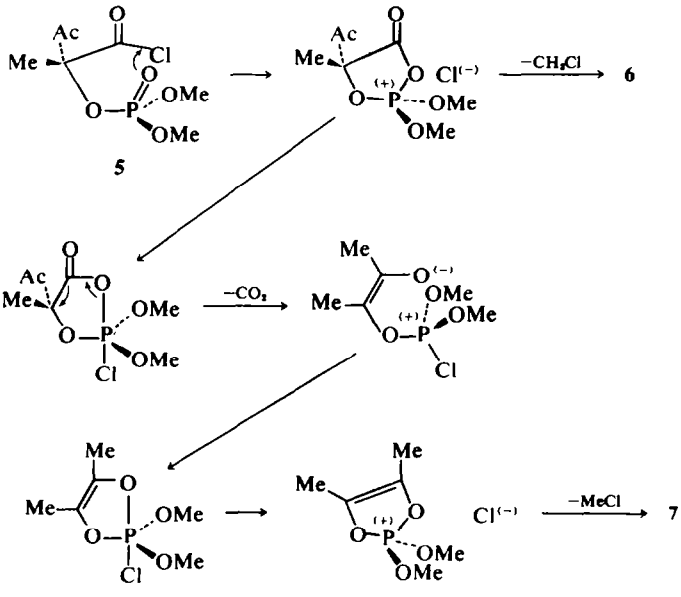
The production of cyclophosphate, **7**, from Me-CAP, **6**, at relatively high temperatures could proceed *via* the transition state shown in Scheme 2.



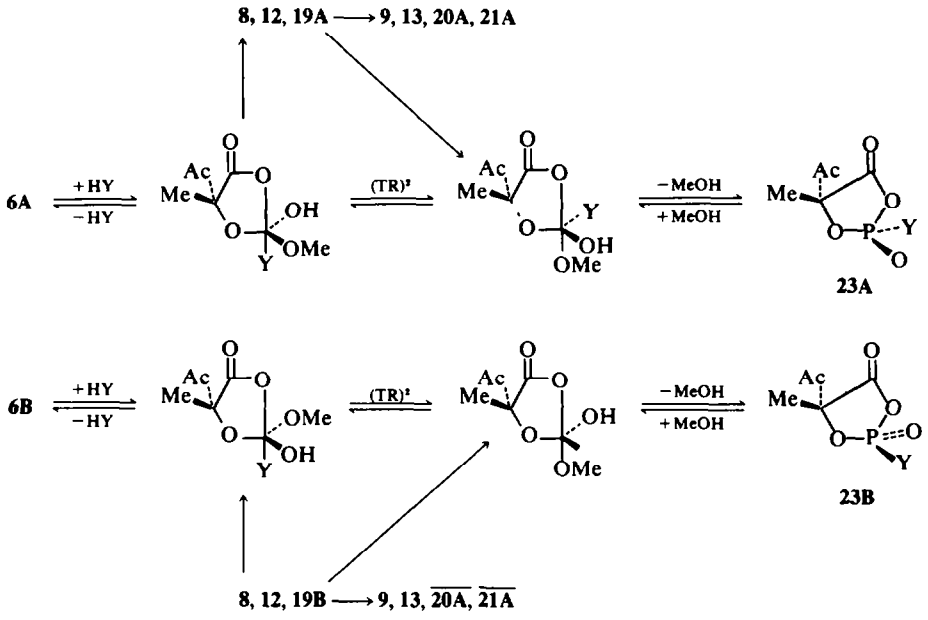
SCHEME 2

The extraordinary reactivity of Me-CAP, **6**, toward water, alcohols and phenols follows from several factors. (1) The high apicophilicity[36] of oxygen-containing nucleophiles, *i.e.*, the ligand Y in Scheme 3. (2) The high apicophilicity[36] of the acyloxy group, —O—CO.R. (3) The stability conferred by the 5-membered ring on oxyphosphoranes,[29c, 31c, d, 32, 34-36] and the preference of this ring for the apical-equatorial skeletal position in P(5).

Since the double TR-process, or $(TR)^2$ in Scheme 3, is a relatively slow process,[34-36] the stereospecificity in the formation of the β-ketoacids, **19A**, from the *cis*-Me-CAP, **6A**, is understandable; *i.e.*,



SCHEME 1

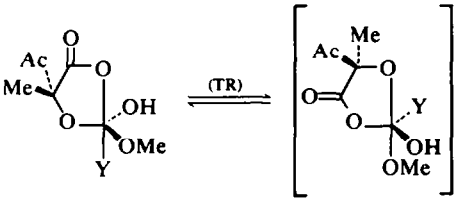


SCHEME 3; Y = OH, MeO, RO.

ring-opening by apical-departure of the acyloxy ligand is favored, and this results in the formation of the ketoacids, *e.g.*, **19A**, with inversion of the P-chirality. The same mechanism applies when there is no P-chirality, as in **6A**→**8** and **12**. (As expected, the chirality at carbon is not preserved in the decarboxylation of the β-ketoacids **19A** to the phosphoacetoins, **20A**+**21A**; see also **6A**→**9** and **13**.)

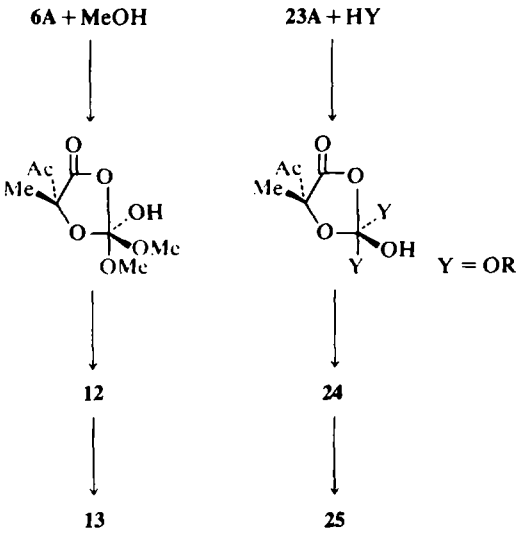
The facile departure of the acyloxy ligand, and the relative difficulty in the $(TR)^2$ process (Scheme 3) also account for the formation of very small amounts of methanol, and of the acid-CAP, (**23A**, Y = OH ≡ **11**), during the hydrolysis of methyl-CAP, **6**. The same is true for the relatively small amounts of transesterification of Me-CAP, **6**, upon reaction with alcohols (ROH) other than methanol. A given stereoisomeric oxyphosphorane with the methoxy and acyloxy ligands in apical positions can be generated in two ways as shown in Scheme 3: (1) By the $(TR)^2$ isomerization of the precursor oxyphosphorane isomer: (2) By recyclization[27b-d] of the methylalkylphosphato-β-ketoacid, **19A**, (or the diastereomer at phosphorus, **19B**). The first mechanism represents a "regular isomerization", and the second, an "irregular isomerization" of P(5).[34-36] The irregular process for recyclization can give rise, in principle, to three P(5)-isomers with Y, MeO, and OH in the apical positions, respectively; however, only the first two isomers are able to yield an alkyl-CAP by apical-departure of an exocyclic ligand. It is not known at present whether the transesterification which was observed in these experiments proceeds by the regular (1), or the irregular (2) mechanism, or by both of these.

The alternate way to effect the transesterification, *i.e.*, by single TR (Scheme 4) requires the movement of the strongly apicophilic[36] acyloxy ligand to an equatorial position of the P(5), and is disfavored.



SCHEME 4

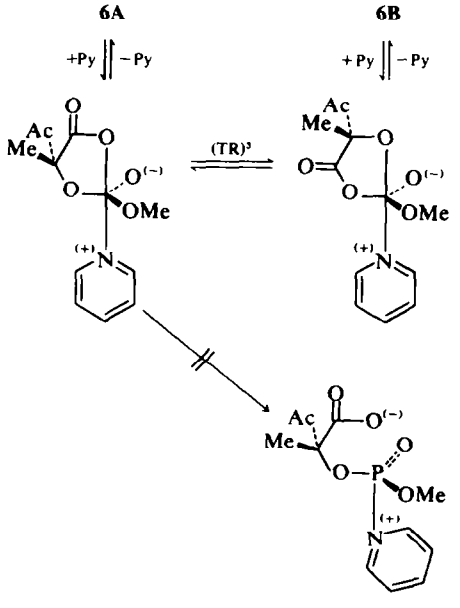
When the reaction of Me-CAP, **6**, with an alcohol, ROH, other than methanol involves a certain amount of transesterification (Scheme 3, **6A**→**23A**), two additional products are expected, in addition to the 2-(methylalkylphosphato)-2-methyl-3-oxobutanoic acid, **19A** (and the corresponding decarboxylation products, **20A**+**21A**, Scheme 3). These new products can originate according to Scheme 5. One of them is dimethylphosphoacetoin, **13**, formed by decarboxylation of **12**, which results, in turn, from the reaction of the original Me-CAP, **6A**, with the methanol formed in the transesterification. The second product is the dialkyl phosphoacetoin, **25**, formed by decarboxylation of **24**; the latter is derived from the reaction of the alcohol, ROH,



SCHEME 5

with the alkyl-CAP, **23A**, which is formed in the transesterification. These by-products are observed, in small amounts, in some of the phosphorylations of ROH by Me-CAP, **6**.

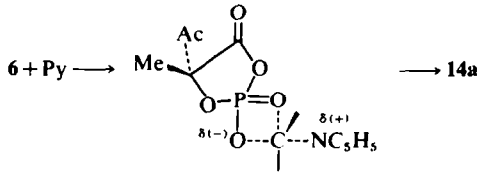
Scheme 6 explains the stereoequilibration of *cis*-Me-CAP: **6A**⇌**6B**, and the preferential attack of the methyl carbon of the methoxy group of **6**, rather than the electrophilic phosphorus by pyridine. The P(5) derived by attack of nitrogen at phosphorus involves charge-separation and ring-opening to a dipolar phosphoramidium species, and is unlikely. This permits the relatively unfavorable triple TR, or



SCHEME 6

(TR)³ to occur. The result of the (TR)³ is stereomutation.

The nucleophilic attack of the pyridine at the Me carbon of **6** (Scheme 7) can be attributed to the fact that the incipient formation of the C—N bond and the simultaneous rupture of the C—O bond are energetically favored over the initial formation of a P—N bond and cleavage of a P—O bond. This argument is based upon an estimate of activation energies by Szabo's method.[41] The result is the N-methylation by Me-CAP (Scheme 7) rather than phosphorylation either *via* a transition state or *via* a P(5) intermediate (*cf* Scheme 6).



SCHEME 7

The stereomutation: **6A**⇌**6B** can also be effected by alcohols *via* a (TR)³ process (*cf* Scheme 6 with RO in place of pyridine). The relative difficulty of effecting a (TR)³ *vs* apical acyloxy departure explains the stereospecificity observed in the phosphorylation of ROH by *cis*-Me-CAP, **6A**, discussed above.

EXPERIMENTAL

2-2-2-Trimethoxy-4,5-dimethyl-2,2-dihydro-1, 3, 2-dioxaphospholene (**4**)

Anhydrous, freshly distilled biacetyl, Me.CO.CO.Me, was added dropwise to a slight excess (*ca* 1·1 molequiv) of trimethyl phosphite (freshly distilled; pretreated with Na ribbon), with stirring. The temp was maintained between 0° and 5° during the addition, and at 25° for an additional 2 hr. The oxyphosphorane, **4**, was obtained in *ca* 95% yield after distillation: b.p. 45–55° (0·2–0·5 mm); singlet at $\tau = 8{\cdot}23$ ppm, and a doublet at $\tau = 6{\cdot}52$ ppm. $J_{HCOP} = 12{\cdot}9$ Hz. The oxyphosphorane, **4**, should be handled and stored under anhydrous conditions, preferably under N_2. It reacts slowly with oxygen to form biacetyl and $(MeO)_3PO$; the biacetyl then reacts very slowly with more oxyphosphorane to generate the 2:1 adduct previously described.[29]

2-(Dimethylphosphato)-2-methyl-3-oxobutanoyl chloride (**5**)

Phosgene (70 ml; 98 g; 1 mole) was transferred to a trap cooled in a Dry Ice-acetone bath, and was led through a tube packed with freshly calcined $CuSO_4$ into the reaction flask, which contained 100 ml of anhyd hexane kept at 0°. Compound **4** (125 g; 0·6 moles) was added to the phosgene-hexane soln, dropwise, over a period of 1 hr, with stirring. Evolution of CH_3Cl was noted, and the ketoacid chloride, **5**, separated as an oil. The mixture was stirred 0·5 hr at 20°, and was evaporated at 40° (30 mm) without exposure to moist air. The residue (154 g) was **5**, as shown by IR, and NMR data[30] (Table 1). This material,

without further purification, was used for the preparation of **6A**+**6B**.

cis-2-*Oxo*/5-*acetyl and* trans-2-*oxo*/5-*acetyl* 2,4-*dioxo*-2-*methoxy*-5-*acetyl*-5-*methyl*-2-*hydro*-1, 3, 2-*dioxaphospholane* or *cyclic anhydride of* 2-(*methylphosphato*)-2-*methyl*-3-*oxobutanoic acid* (Me-CAP's, **6A** and **6B**)

Compound **5** (0·1 mole) was mixed with 3 ml of anhyd di-n-butyl phthalate (to act as a "chaser" in the subsequent distillation) and a catalytic amount (*ca* 2 mole %) of freshly calcined $CuSO_4$, in a reaction vessel suitable for short-path distillation. The vessel was evacuated to *ca* 5 mm, and was immersed in a bath preheated to 100°, while the mixture was being stirred. Loss of methyl chloride occurred at once, and distillation commenced soon thereafter. The fraction boiling below 80° (at *ca* 1 mm) was rejected, and the fraction which distilled subsequently was collected, mostly in the b.p. range 104–107° (1–0·5 mm; bath at 100–120°). (Higher temps should be avoided during the distillation, since **6** is relatively thermally unstable; however, to collect the last portions of distillate, the bath-temp may be allowed to reach 140°). This procedure afforded about 90% of the expected yield of distillate (based on the m.w. of **6**); spectrometric analysis (Table 1) showed that the distillate consisted of 75% of a mixture of **6A** and **6B**; *ca*: 70:30 proportion. The material balance consisted of **7**, and a mixture of **9** and **13**. For the preparation of N-methylpyridinium-CAP (see below), the above mixture of **6A**+**6B**, is satisfactory. The pure **6A**, was obtained as follows. Diethyl ether was added to the non-crystalline mixture (50% by volume of distillate) and this phase was seeded with crystalline **6A**. The resulting crystals were filtered and washed with small volumes of ether to give pure **6A** in *ca* 35% of the theoretical yield based on **5**. The combined ether phases yielded an impure mixture of **6A**+**6B**, enriched in the latter. This was converted into the N-methylpyridinium-CAP (*ca* 30% yield based on **5**) as described below.

Crystalline **6A** had m.p. 82–84° (CH_2Cl_2); the NMR signals are listed in Table 1; and IR spectrum had the following bands (in cm^{-1}): 1838, 1748, 1445, 1316, 1190, 1136, 1087, 1064–1042, 1010, 990, 952, 909 and 877. (Found: C, 34·2; H, 4·8; P, 14·6. Calcd. for $C_6H_9O_6P$: C, 34·6; H, 4·4; P, 14·9%.)

Due to the extraordinary reactivity of **6**, the analytical data must be obtained under anhyd conditions.

(The original **5** is hydrolyzed very rapidly to **12**, which decarboxylates to **13**; the appearance of small amounts of the latter as a by-product in the synthesis of **6**, is indicative of water contamination.)

Pyrolysis of the acid chloride (**5**) *in the absence of* $CuSO_4$

(a) The pure **5** was heated to 120° under Ar, and the ^1H NMR spectrum was examined at various intervals. After 1 hr, there was only *ca* 40% decomposition of **5**. After 2 hr, there was 100% decomposition; the product consisted of a mixture of **6A**+**6B** and **7** in roughly equal amounts. This mixture was submitted to short path distillation (bath at 85–95°; 1 mm) giving a distillate in *ca* 80% of the theory. On standing, crystalline **6A**, (30% of theory) separated from the distillate. The CAP was collected by filtration and was washed with cold ether to remove traces of **7**.

(b) The thermal decomposition of **5** was relatively slow in solvents. An 0·85 M soln of **5** in toluene underwent *ca* 20% decomposition after 2 hr at 110°. A 1 M soln of **5** in chlorobenzene underwent *ca* 20% decomposition after 2 hr at 120°.

Pyrolysis of methyl-CAP (**6**)

(a) A sample of **6A**+**6B** kept 2 hr at 150° under Ar was completely transformed into **7**.

(b) There was less than *ca* 20% decomposition when the sample of **6A**+**6B** was kept 2 hr at 120°. At this temp, solvents (e.g. chlorobenzene) did not affect the pyrolysis significantly.

Stereoisomerization of cis-*oxo*/*acetyl methyl-CAP* (**6A**)

(a) A freshly prepared soln of crystalline **6A** in $CDCl_3$ was treated with 5 mole % of *anhydrous* pyridine at 25°. Within 2 min, an equilibrium mixture of 70%-*cis* (**6A**): 30%-*trans* (**6B**) oxo/acetyl methyl-CAP's was established according to the ^1H NMR spectrum (Table 1).

(b) In the absence of pyridine, the establishment of the same equilibrium required *ca* 20 hr.

Reaction of methyl-CAP (**6**) *with water*

(a) *In* CH_2Cl_2, *followed by diazomethane.* One molequiv of water (0·083 ml) was added to a 1·15 M methylene chloride soln of **6** (0·96 g in 4 ml), at 25°, with stirring. The soln was quickly (*ca* 2 min) treated with a slight excess of ethereal diazomethane. The resulting **10** (Table 1) was isolated as described below.

(b) *In dioxane-*D_8. One molequiv of water was added to a 0·67 M dioxane-D_8 soln of **6**, at 25°, with stirring. The ^1H NMR spectrum was recorded after *ca* 15 sec, and after various time-intervals; the results are listed in Tables 1 and 2. The initial major product was **8**, which was accompanied by traces of MeOH (and presumably of **11**). The ^1H NMR signal of MeOH and the signals of **8**, persisted for at least 1 hr; then, the appearance of the signals of **9**, from the decarboxylation of **8**, became noticeable.

(c) *In* $CDCl_3$. One molequiv of water was added to a 1·8 M $CDCl_3$ soln of **6**, at 25°, with stirring. At this concentration, **8** was sparingly soluble and separated as a gel.

(d) *In benzene.* A slight excess of water (1·3 molequiv) was added to a 1·5 M benzene soln of **6** at 25°, with stirring. The initial gel that separated turned into a clear soln as decarboxylation proceeded and **9** was formed.

Reaction of methyl-CAP **6**) *with methanol*

(a) *In* CH_2Cl_2 *followed by diazomethane.* One molequiv of MeOH (0·218 ml) was added to a 1·1 M methylene chloride soln of **6** (1·12 g in 5 ml) *at* 0°, with stirring. The mixture was quickly treated with ethereal diazomethane, and was then evaporated at 40° (20 mm). Short path distillation (b.p. *ca* 100° at 0·1 mm) of the residue afforded **10** (Table 1). (Found: C, 37·7; H, 6·1; P, 12·4. Calcd. for $C_8H_{15}O_7P$: C, 37·8; H, 5·9; P, 12·2%.)

(b) *In* $CDCl_3$. One molequiv of MeOH (0·05 ml) was added to a 1·25 M $CDCl_3$ soln of **6** (0·26 g in 1 ml), at 0°, with stirring. The ^1H NMR spectrum disclosed the intermediate formation of **12** (Table 1). The soln was kept at 25° until the CO_2 evolution was complete at which point the spectrum was that of **13**[33] (Table 1).

(c) *In benzene.* Dimethyl phosphoacetoin[33] (**13**) was isolated as the final product of the reaction of 1 molequiv of MeOH with methyl-CAP in a 0·26 M benzene soln, at 25°.

Rates of reaction of methyl-CAP and of methyl acetoinenediol cyclophosphate with water, alcohols and phenols

The procedure used and the results obtained are given in Table 2.

Reaction of methyl-CAP (**6**) *with pyridine. Preparation of* N-*methylpyridinium* 2,4-*dioxo*-2-*oxy*-5-*acetyl*-5-*methyl*-2-*hydro*-1,3,2-*dioxaphospholane* (N-*methyl-pyridinium-CAP*, **14a**)

(a) *In* CH_2Cl_2 *and in* $CDCl_3$. One molequiv of *anhydrous* pyridine was added to a 2 M soln of **6** in these solvents, at 25°, with stirring. The NMR spectra of the solns, examined after 1 hr, showed the complete conversion of **6** into **14a**, (Table 1).

(b) *In benzene.* A soln of **6** (2·28 g; 11·3 mmoles) in benzene (14 ml) was treated, dropwise, with pyridine (1·0 ml; 1·1 molequiv), at 25°. The **14a** separated as a colorless, viscous oil in *ca* 95% yield, and was freed from benzene by decantation. The salt was stored under Ar for further use; it was soluble in methylene chloride, acetonitrile and pyridine; the NMR data are summarized in Table 1.

Reaction of N-*methylpyridinium-CAP*, **14a**, *with trimethyloxonium tetrafluoroborate*

A 4 M methylene chloride soln of **14a** was prepared as described above, and was treated with one molequiv of the methylating agent. After the evolution of dimethyl ether had ceased, the solution was analyzed by NMR spectrometry, and showed the regeneration of **6** and the presence of the N-methylpyridinium cation.

Reaction of methyl-CAP (**6**) *with other tertiary amines*

The amine [γ-picoline (1 molequiv); trimethylamine (1·7 molequiv)] was added to a 0·7 M solution of **6** in benzene, at 25° with stirring. The resulting salts, **14b**, **14c**, had enough solubility in the benzene or in the benzene plus excess of amine soln (in the case of the tetramethylammonium salt) to give the ^1H NMR signals listed in Table 1.

Reaction of pyridine with acetyldimethyl phosphate

One molequiv of pyridine was added to a 1·67 M $CDCl_3$-soln of acetyldimethyl phosphate,[18] at 25°. After 48 hr, only *ca* 30% of the phosphate had reacted as shown by the appearance of the signal at $\tau = 5{\cdot}44$ ppm due to the N-methylpyridinium cation. After 5 days the reaction appeared to be complete.

Reaction of N-*methylpyridinium-CAP*, **14a**, *with water and with methanol*

The reagent was added to a soln of **14a** in $CDCl_3$ or in CH_2Cl_2, at 25°, with stirring. The evolution of CO_2 began immediately, and ceased within 10 min.

(*a*) *Water.* The addition of one molequiv of water yielded N-methylpyridinium phosphoacetoin (**16a**; Table 1).

(*b*) *Methanol.* The addition of one molequiv, or of an excess, of methanol yielded **18** (Table 1).

The phosphorylation of the alcohol was also carried out in pyridine as solvent.

Reaction of cis-*methyl-CAP* (**6A**) *with alcohols other than methanol*

Three types of experiments were carried out.

(1) One molequiv of the alcohol was added to a 1·0M $CDCl_3$ soln of freshly crystallized **6A** at 0°, with stirring. The ^1H NMR spectrum was examined as quickly as possible (*ca* 15 sec), and after various time-intervals, until no further changes were noted; the signals due to the intermediate β-ketoacids and the final alkylmethyl phosphoacetoins are given in Table 1.

(2) As above, but the soln was heated to 80° after the reagents were mixed. The soln was analyzed by NMR spectrometry, and was then evaporated to isolate the corresponding alkylmethyl phosphoacetoin which resulted from decarboxylation of the intermediate β-ketoacid; (Table 1). The alcohol was added to **6A** as above, in CH_2Cl_2 or CCl_4 at 0°, with stirring. The resulting soln was immediately treated with ethereal diazomethane. The soln was evaporated and the methyl 2-(methylalkylphosphato)-2-methyl-3-oxobutanoate was isolated by short-path vacuum distillation, whenever possible. The NMR signals are given in Table 1.

The elemental analyses obtained on phosphate esters made by these procedures are:

(*a*) *From ethanol.* Compound **22A** R = Et); b.p. *ca* 100° (0·1 mm). (Found: C, 40·6; H, 6·5; P, 11·6. Calcd. for $C_{15}H_{17}O_7P$: C, 40·3; H, 6·4; P, 11·7%.)

(*b*) *From* iso-*propyl alcohol.* Compound **20A** + **21A** (R = iso-Pr, analysis of undistilled product). (Found: C, 42·9; H, 7·8; P, 13·7. Calcd. for $C_8H_{17}O_5P$: C, 42·8; H, 7·6; P, 13·8%.)

Acknowledgement—F. R. acknowledges the support of these investigations by the Cancer Institute of the U.S. Public Health Service (Grant CA-04769) and by the National Science Foundation (USA) (Grant GP-6690). I. U. acknowledges the support of the National Science Foundation (USA) (Grant GP-28927X), and of the Biomedical Sciences Support of the U.S. National Institute of Health (Grant RR07012).

REFERENCES

[1]H. Kammerer and L. Carius, *Liebigs Ann.* **131**, 153 (1864)
[2]F. Lynen, *Ber. Dtsch. Chem. Ges.* **73**, 367 (1940)
[3a]F. Lipmann and L. C. Tuttle, *J. Biol. Chem.* **153**, 751 (1944); [3b]E. R. Stadman and F. Lipmann, *Ibid.*, **185**, 549 (1950)
[4]R. Bentley, *J. Am. Chem. Soc.* **70**, 2183 (1948)
[5]D. R. Phillips and T. H. Fife, *Ibid.* **90**, 6803 (1968)
[6a]D. E. Koshland, Jr., *Ibid.* **73**, 4103 (1951); [6b]D. E. Koshland, *Ibid.* **74**, 2286 (1952)
[7]J. H. Park and D. E. Koshland, Jr., *J. Biol. Chem.* **233**, 986 (1958)
[8]G. DiSabato and W. P. Jencks, *J. Am. Chem. Soc.* **83**, 4393 (1961)
[9]T. C. Buice and S. J. Benkovic, *Bioorganic Mechanisms* Vol. 2, p. 21. Benjamin, New York (1966)
[10]H. Chantrenne, *Biochim. Biophys. Acta* **2**, 286 (1948)
[11]N. S. Corby, G. W. Kenner and A. R. Todd, *J. Chem. Soc.* 1234 (1952)
[12]T. Wieland and F. Jaenieke, *Liebigs Ann.* **613**, 95 (1958)
[13]H. G. Khorana and J. P. Vizsolyi, *J. Am. Chem. Soc.* **81**, 4660 (1959)
[14]W. P. Jencks and J. Carrivolo, *J. Biol. Chem.* **234**, 1272, 1280 (1959)
[15]R. R. Whetstone, U.S. 2,648,696 (1954); *Chem. Abstr.* **48**, 8250i (1954)
[16]A. W. D. Avison, *J. Chem. Soc.* 732 (1955)
[17]K. A. Petrov and A. A. Neimysheva, *Zh. Obshch. Khim.* **29**, 1822 (1959)
[18a]F. Cramer and K. G. Gartner, *Chem. Ber.* **91**, 704 (1958); [18b]F. Cramer and K. G. Gartner, U.S. 2,939,876 (1961); *Chem. Abstr.* **55**, 6443f (1961); [18c]F. Cramer, *Agnew. Chem.* **72**, 236 (1960)
[19]V. P. Evdakov and E. K. Shlenkova, *Dopl. Akad. Nank. SSSR* 168(6), 1323 (1966)
[20]D. M. Brown, *Advances in Organic Chemistry* Vol. 2, p. 141 Interscience New York (1963)

[21]V. M. Clark, D. W. Hutchinson, A. J. Kirby and S. G. Warren, *Angew. Chem.* **76**, 704 (1964)
[22a]F. Cramer, *Ibid., Internat. Edit.* **5**, 173 (1966); [b]F. Cramer, R. Helbig, H. Hettler, H. K. Scheit and H. Seliger, *Ibid.* **78**, 640 (1966); *Ibid.* Internat. Edit., **5**, 601 (1966)
[23]H. G. Khorana, *Pure Appl. Chem.* **17**, 349 (1968)
[24]K. L. Argawal, A. Yamazaki, P. J. Cashion and H. G. Khorana, *Angew. Chem.* **84**, 489 (1972); *Ibid.* Internat. Edit. **11**, 451 (1972)
[25]M. L. Bender and J. M. Lawlor, *J. Am. Chem. Soc.* **85**, 3010 (1963)
[26]J. F. Marecek and D. L. Griffith, *Ibid.* **92**, 917 (1970)
[27a]V. M. Clark and A. J. Kirby, *Ibid.* **85**, 3705 (1963); [b]S. J. Benkovic and K. J. Schray, *Biochem.* **7**, 4090 (1968); [c]J. Benkovic and K. J. Schray, *Ibid.* **7**, 4097 (1968); [d]K. J. Schray and S. J. Benkovic, *J. Am. Chem. Soc.* **93**, 2522 (1971); [e]G. M. Blackburn and M. J. Brown, *Ibid.* **91**, 525 (1969)
[28]F. Ramirez, S. Glaser, P. Stern, P. D. Gillespie and I. Ugi, *Angew. Chem.* **85**, 39 (1973); *Ibid.* Internat. Edit. **12**, 66 (1973)
[29a]F. Ramirez and N. B. Desai, *J. Am. Chem. Soc.* **82**, 2652 (1960); [b]F. Ramirez, A. V. Patwardhan, N. Ramanathan, N. B. Desai, C. V. Greco and S. R. Heller, *Ibid.* **87**, 543 (1965); [c]F. Ramirez, *Accounts Chem. Res.* **1**, 168 (1968)
[30]F. Ramirez, S. B. Bhatai, A. J. Bigler and C. P. Smith, *J. Org. Chem.* **33**, 1192 (1968)
[31a]F. Ramirez, N. Ramanathan and N. B. Desai, *J. Am. Chem. Soc.* **85**, 3465 (1963); [b]F. Ramirez, A. V. Patwardhan, N. B. Desai and S. R. Heller, *Ibid.* **87**, 549 (1965); [c]F. Ramirez, *Bull. Soc. Chim. Fr* 2443 (1966); [d]F. Ramirez, *Ibid.* 3491 (1970)
[32a]F. Ramirez, O. P. Madan and C. P. Smith, *J. Am. Chem. Soc.* **87**, 670 (1965); [b]D. Swank, C. N. Caughlan, F. Ramirez, O. P. Madan and C. P. Smith, *Ibid.* **89**, 6503 (1967)
[33]F. Ramirez, B. Hansen and N. B. Desai, *Ibid.* **84**, 4588 (1962)
[34]P. Gillespie, P. Hoffman, H. Klusacek, D. Marquarding, S. Pfohol, F. Ramirez, E. A. Tsolis and I. Ugi, *Angew. Chem.* **83**, 691 (1971); *Ibid.* Internat. Edit. **10**, 687 (1971)
[35a]F. Ramirez and I. Ugi, *Advances in Physical Organic Chemistry* (Edited by V. Sold) Vol. 9, p. 25, Academic Press, London (1971); [b]I. Ugi and F. Ramirez, *Chemistry in Britain* **8**, 198 (1972)
[36]P. Gillespie, F. Ramirez, I. Ugi and D. Marquarding, *Angew. Chem.*, **85**, 99 (1973); *Ibid.* Internat. Edit. **12**, 91 (1973)
[37]W. E. McEwen, *Topics in Phosphorus Chemistry* (Edited by M. Grayson and E. J. Griffith) Vol. 2, p. 1. Interscience, N.Y. (1965)
[38]F. H. Westheimer, *Accounts Chem. Res.* **1**, 70 (1968)
[39]K. Mislow, *Ibid.* **3**, 321 (1970).
[40]R. F. Hudson and C. Brown, *Ibid.* **5**, 204 (1972)
[41a]Z. G. Szabo, *Magy. Ind. Akad. Kem. Ind. Oszt.* Koslem **19**, 291, 303 (1963); [b]Z. G. Szabo, *Z. Phys. Chem.* NF **55**, 1 (1967); [c]Z. G. Szabo and T. Berces, *Ibid.* **57**, 38 (1968)