

*Anal.* (for **8**). Calcd for  $C_{19}H_{16}O_2S_2$ : C, 61.27; H, 4.33. Found: C, 61.35; H, 4.31.

This same reaction repeated in 10 ml of DMF (10 ml) containing 0.5 ml (12 mmol) of methanol with 600 mg of potassium thiophenoxide and 500 mg (1.6 mmol) of **5a** at 70° for 30 min gave a 65:35 mixture of **6** and **7**, respectively, while in a 50:50 mixture of methanol-DMF (5 ml each), **5a** gave only **7** in near quantitative yield.

**Reaction of  $\alpha$ -Chlorobenzyl Phenyl Sulfone (**5b**) with Potassium Thiophenoxide in DMF and Methanol-DMF.**—Reaction of **5b**<sup>27</sup> with potassium thiophenoxide in DMF and in 50% methanol-DMF was carried out in the same manner as that of **5a** and gave identical results. In 5% methanol-DMF the reaction was performed in the same manner as that of **5a** but gave instead 80% **6** and 20% **7** (nmr analysis).

**Reaction of **1b** with Sodium Ethoxide in Ethanol.**—To a solution of 400 mg of sodium metal dissolved in 20 ml of absolute ethanol was added 500 mg (2.6 mmol) of **1b**. This mixture stood at reflux for 18 hr and was then worked up as usual. An nmr spectrum of the resulting oil showed about a 4:1 mixture of recovered **1b** and methyl phenyl sulfone (**3**). The spectrum was contaminated with several smaller peaks which were not readily identifiable.

**Reaction of **1a** with Piperidine in DMF.**—A mixture of 300 mg (1.29 mmol) of **1a** and 200 mg (2.35 mmol) of piperidine were held at 70–80° for 10 hr in 15 ml of dry DMF. The mixture was poured into water and extracted with ether. An

nmr spectrum of the crude reaction mixture showed **1a** and piperidine present. When the piperidine was removed by washing with dilute hydrochloric acid, a small amount of methyl phenyl sulfone (**3**) was visible in the nmr spectrum. Crystallization from ethanol of the crude reaction mixture after removal of the piperidine gave 240 mg (80%) of recovered **1a**.

**Determination of the Relative Rates of Reaction of **5a** and **5b** with Thiophenoxide Ion.**—Aliquots (5 ml) were taken of a solution of 625 mg (2.0 mmol) of **5a** in 20 ml of dry DMF to which 445 mg (3.0 mmol) of potassium thiophenoxide in 20 ml of dry DMF had been added. The first aliquot (1 min) showed no **5a** present (nmr analysis). This same procedure with **5b** (515 mg, 2.0 mmol) showed that the reaction was not complete for ca. 10 hr (therefore  $k_{Br}/k_{Cl} > 600$ ).

The procedure for 50% methanol-50% DMF was as follows. To a solution of 315 mg (1.0 mmol) of **5a** in 10 ml of DMF and 7 ml of methanol was added 3 ml of a solution of 120 mg (5.2 mg-atoms) of sodium metal and 550 mg (5.0 mmol) of benzenethiol dissolved in 10 ml of methanol (1.5 mmol of sodium thiophenoxide added). The half-life of this reaction was ca. 1 hr. Under these same conditions, **5b** showed no sign of reaction (nmr analysis) after 27 hr.

**Registry No.**—**2**, 15296-86-3; **3**, 3112-85-4; **4**, 4832-52-4; **5a**, 15296-88-5; **7**, 3112-88-7; **8**, 15296-89-6.

**Acknowledgment.**—We are grateful to the National Science Foundation for support of this work (GP 4208).

(27) R. Otto, *J. Prakt. Chem.*, **40**, 505 (1889).

## $\alpha,\beta$ -Unsaturated Aldehydes as Acceptors in the Oxyphosphorane Carbon-Carbon Condensation. Hydrolyses of Five-Membered Cyclic Pentaoxyphosphoranes and Phosphate Esters<sup>1</sup>

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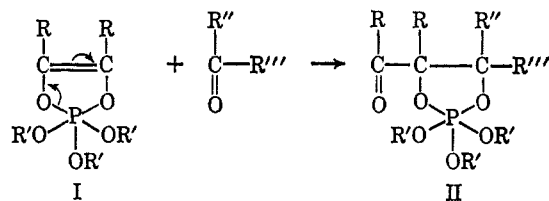
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2,2,2-Trimethoxy-4,5-dimethyl-2,2-dihydro-1,3,2-dioxaphospholene performed a nucleophilic 1,2 addition to the carbonyl function and not a 1,4 addition to the olefinic carbon of acrolein. The product was 2,2,2-trimethoxy-4 $\beta$ -methyl-4 $\alpha$ -acetyl-5 $\alpha$ -vinyl-2,2-dihydro-1,3,2-dioxaphospholane; only the diastereomer with a *cis*-CH<sub>2</sub>/H was obtained. Hydrolysis of the five-membered pentaoxyphosphorane gave the two diastereomers at phosphorus of the five-membered cyclic phospho triester. The cyclic phospho triesters underwent an extraordinarily rapid reaction with methanol and gave the corresponding open-chain phospho triester derived from a  $\gamma$ -unsaturated  $\alpha,\beta$ -dihydroxy ketone. The kinetically controlled product had the phosphate at the  $\alpha$  position, but the thermodynamically stable product had the phosphate at the  $\beta$  position. The open phospho triester regenerated the cyclic phospho triester upon distillation under vacuum. Hydrolysis of the five-membered pentaoxyphosphorane with an excess of water gave minor amounts of the open-chain  $\beta$ -phospho triester and major amounts of the open phospho monoester derived from the  $\gamma$ -unsaturated  $\alpha,\beta$ -dihydroxy ketone. The kinetically controlled product had the dihydrogen phosphate group at the  $\alpha$  carbon, while the thermodynamically stable product had the dihydrogen phosphate group at the  $\beta$  carbon. The five-membered cyclic phospho triester underwent a very rapid hydrolysis with 1 mol equiv of water and gave the five-membered cyclic phospho diester and the open-chain  $\beta$ -phospho triester.

The nucleophilic addition<sup>3</sup> of 2,2,2-trialkoxy-2,2-dihydro-1,3,2-dioxaphospholenes<sup>4</sup> (**I**) to the carbonyl group of mono- and polycarbonyl compounds constitutes a new and a stereoselective method of making

carbon-carbon bonds. This reaction, which can be conveniently named the *oxyphosphorane condensation*,<sup>3</sup> produces derivatives of the 2,2-dihydro-1,3,2-dioxaphospholane ring system, **II**.



vious discovery of the attack by the phosphorus of trialkyl phosphites on the oxygen of *p*-quinones: cf. (d) F. Ramirez and S. Dershowitz, *J. Org. Chem.*, **22**, 856 (1957); (e) F. Ramirez and S. Dershowitz, *ibid.*, **23**, 778 (1958).

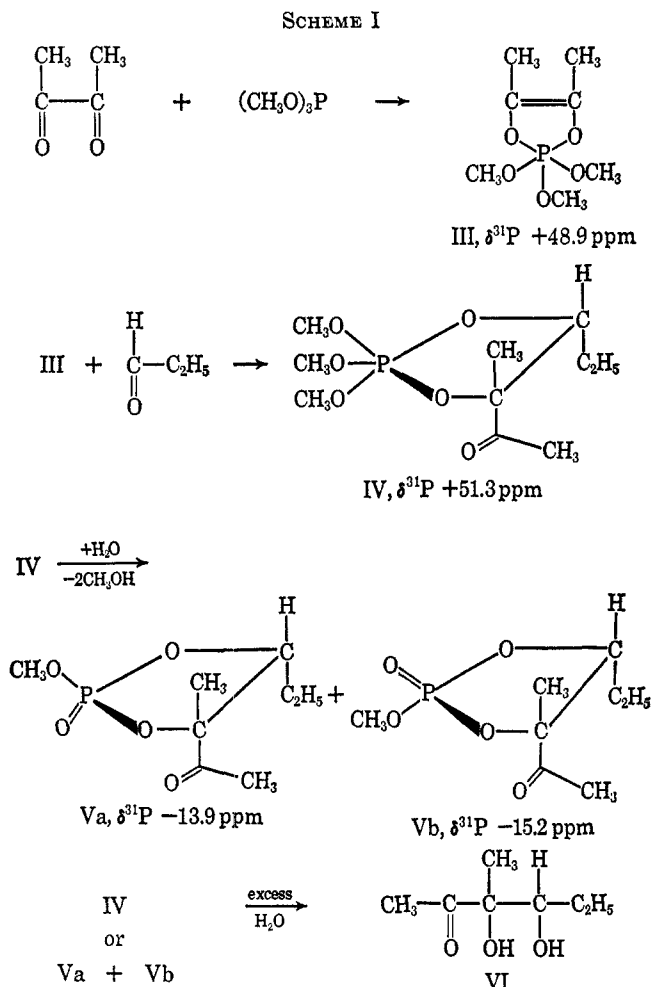
(1) Part XXXVIII: Organic Compounds with Pentavalent Phosphorus.

(2) This investigation was supported by Public Health Service Grant CA-04769 from the National Cancer Institute and by the National Science Foundation, Grants GP-3341 and GP-6690-Y.

(3) (a) F. Ramirez and N. Ramanathan, *J. Org. Chem.*, **26**, 3041 (1961); (b) F. Ramirez, N. Ramanathan, and N. B. Desai, *J. Amer. Chem. Soc.*, **84**, 1317 (1962); (c) F. Ramirez, *Pure Appl. Chem.*, **9**, 337 (1964); (d) F. Ramirez, *Bull. Soc. Chim. Fr.*, 2443 (1966).

(4) Derivatives of the 2,2-dihydro-1,3,2-dioxaphospholenes like **III** were first described by three groups of investigators: (a) G. H. Birum and J. L. Dever, Abstracts, Division of Organic Chemistry, 135th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1958, p 101-P; (b) V. A. Kukhtin, *Dokl. Akad. Nauk SSSR*, **121**, 466 (1958); *Chem. Abstr.*, **53**, 1105b (1959); (c) F. Ramirez and N. B. Desai, *J. Amer. Chem. Soc.*, **82**, 2650 (1960). Our discovery of phospholenes **III** from the reactions of trialkyl phosphites with *o*-quinones and  $\alpha$ -diketones was based on our pre-

The cyclic, saturated pentaoxyphosphoranes can be hydrolyzed to five-membered cyclic phosphate esters, to open-chain phosphate esters, and to phosphorus-free polyhydroxycarbonyl compounds related to the carbohydrates.<sup>5</sup> For example, the condensation of the  $\alpha$ -diketone, biacetyl, with propionaldehyde can be effected by means of trialkyl phosphites according to the sequence of reactions<sup>6</sup> (III  $\rightarrow$  IV  $\rightarrow$  Va + Vb  $\rightarrow$  VI) given in Scheme I.



This paper describes the behavior of  $\alpha,\beta$ -unsaturated aldehydes in the oxyphosphorane condensation. We wished to determine whether the dioxaphospholenes are capable of performing a 1,2 addition to the carbonyl function of  $\alpha,\beta$ -unsaturated aldehydes or whether such an addition is of the Michael reaction type, *i.e.*, a 1,4 addition to the olefinic carbon of the unsaturated aldehyde.

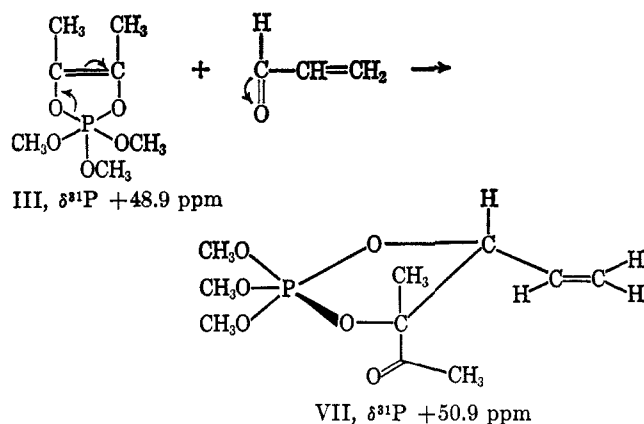
## Results

**Reaction of 2,2,2-Trimethoxy-4,5-dimethyl-2,2-dihydro-1,3,2-dioxaphospholene (III) with  $\alpha,\beta$ -Unsaturated Aldehydes.**—Phospholene III reacted with 1 mol equiv of acrolein at 0°. The product of this

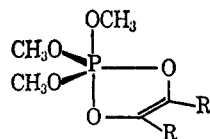
(5) (a) F. Ramirez, N. B. Desai, and N. Ramanathan, *J. Amer. Chem. Soc.*, **85**, 1874 (1963); (b) F. Ramirez, A. V. Patwardhan, N. B. Desai, N. Ramanathan, and C. V. Greco, *ibid.*, **85**, 3056 (1963); (c) F. Ramirez, N. Ramanathan, and N. B. Desai, *ibid.*, **85**, 3465 (1963).

(6) (a) F. Ramirez, A. V. Patwardhan, N. Ramanathan, N. B. Desai, C. V. Greco, and S. R. Heller, *ibid.*, **87**, 543 (1965); (b) F. Ramirez, A. V. Patwardhan, N. B. Desai, and S. R. Heller, *ibid.*, **87**, 549 (1965).

reaction, which was isolated in 90% yield, was 2,2,2-trimethoxy-4 $\beta$ -methyl-4 $\alpha$ -acetyl-5 $\alpha$ -vinyl-2,2-dihydro-1,3,2-dioxaphospholane (VII). The phospholane structure, VII, was based on the following data.



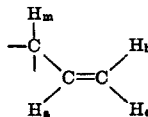
(1) The  $^{31}\text{P}$  nmr shift was strongly positive relative to  $\text{H}_3\text{PO}_4$  and was very similar to that of the biacetyl-propionaldehyde phosphite adduct,<sup>6</sup> IV. A positive  $^{31}\text{P}$  nmr shift of this magnitude is characteristic of pentaoxyphosphoranes.<sup>3-6</sup> The X-ray analysis<sup>7</sup> of one of these compounds showed that the phosphorus was at the center of a trigonal bipyramid, VIII. The apical P-O bonds were longer than the corresponding equatorial P-O bonds. The apical P-O bond associated with the phospholene ring was longer than the apical P-O bond leading to the alkoxy group. Likewise, the equatorial P-O bond associated with the ring was longer than the equatorial P-O bond leading to the alkoxy groups. These observations suggested that (a) the equatorial bonds had more s character than the apical bonds and thus were somewhat shorter, (b) the P-O bonds associated with the phospholene ring had less p-d  $\pi$  bonding than those leading to the alkoxy groups.<sup>7</sup> The former would be longer since the  $\pi$  bonding should result in bond shortening. The decrease in p-d  $\pi$  bonding could result from delocalization of the unshared electrons of the oxygens into the ring rather than into the d orbitals.



(2) The  $^1\text{H}$  nmr spectrum of the oxyphosphorane VII is summarized in Table I. The acetyl group on the phospholane ring was assumed to be in a *cis* relationship to the vinyl group by analogy to the configuration assigned previously to the oxyphosphorane IV made from propionaldehyde. The condensation of the phospholene III with the saturated and the unsaturated aliphatic aldehydes gave only one stereomer in high yield. The condensation of phospholene III with benzaldehyde gave two stereomers, but one of them greatly predominated.<sup>6</sup> The major isomer was assigned the configuration with a *cis*-acetyl/phenyl relationship because the nmr signal due to the

(7) (a) W. C. Hamilton, S. J. LaPlaca, and F. Ramirez, *ibid.*, **87**, 127 (1965); (b) W. C. Hamilton, S. J. LaPlaca, F. Ramirez, and C. P. Smith, *ibid.*, **89**, 2268 (1967); (c) R. D. Spratley, W. C. Hamilton, and J. Ladell, *ibid.*, **89**, 2272 (1967).

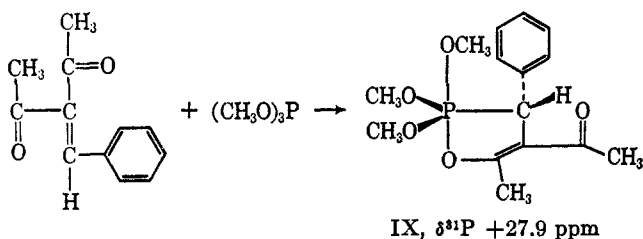
TABLE I  
 $^1\text{H}$  NMR SIGNALS FOR THE TRIMETHOXY BIACETYLACROLEIN  
 PHOSPHITE ADDUCT, VII

$\tau^a$	No. of $^1\text{H}$	$J$ , cps	Assignment
8.62	3		$\text{CH}_3\text{C}$
7.88	3		$\text{CH}_2\text{CO}$
6.42	9	$J_{\text{HP}} = 12.5$	$\text{CH}_2\text{OP}$
			
5.88	1	$J_{\text{HP}} = 7.0$	$\text{H}_m$
4.42	1	$J_{\text{ab}} = 15.0$ $J_{\text{ac}} = 8.1$	$\text{H}_a$
4.96	1	$J_{\text{bc}} = 2.8$	$\text{H}_b$
4.90	1		$\text{H}_c$

<sup>a</sup>  $\tau$  in parts per million vs. TMS = 10.

acetyl protons was at a higher magnetic field in the major isomer. It was assumed that the strong shielding effect of the *cis*-phenyl was responsible for this effect. As expected, the nmr signal due to the methyl protons was at a higher magnetic field in the minor isomer (*cis*-methyl/phenyl).

The three methoxy groups attached to the phosphorus were magnetically equivalent or indistinguishable since they gave only one doublet. The doublet is due to coupling of the protons with the phosphorus. The apparent magnetic equivalency of the three methoxy groups is a general phenomenon among five-membered cyclic pentaoxyphosphoranes<sup>3-6</sup> in solution at 20°. In a few instances in which the  $^1\text{H}$  nmr spectrum has been examined at -70°, the same phenomenon was observed. Apparently, a rapid positional exchange occurred among the groups of the trigonal bipyramid as the result of pseudo-rotation.<sup>8,9</sup> It was shown recently<sup>10a,b</sup> that the three methoxy groups of a related cyclic tetraoxyalkylphosphorane,<sup>10c</sup> IX, which were equivalent at 20°, became nonequivalent at -65°.



(3) The infrared spectrum was consistent with structure VII.

Pentaoxyphosphorane VII was remarkably stable in methanol solution. The  $^{31}\text{P}$  nmr spectrum of a

(8) (a) R. S. Berry, *J. Chem. Phys.*, **32**, 933 (1960); (b) E. L. Muettterties and R. A. Schunn, *Quart. Rev. (London)*, **20**, 245 (1966), and references therein.

(9) NOTE ADDED IN PROOF.—The stereochemistry of the oxyphosphoranes is discussed further by F. Ramirez, J. F. Pilot, O. P. Madan, and C. P. Smith, *J. Amer. Chem. Soc.*, **90**, 1275 (1968), and F. Ramirez, J. F. Pilot, and C. P. Smith, *Tetrahedron*, in press.

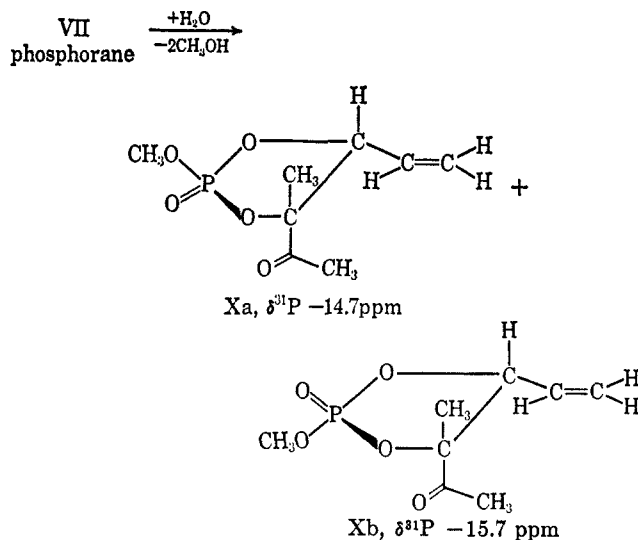
(10) (a) D. G. Gorenstein and F. H. Westheimer, *J. Amer. Chem. Soc.*, **89**, 2762 (1967); (b) F. Ramirez, *Trans. N. Y. Acad. Sci.*, in press; (c) F. Ramirez, O. P. Madan, and S. R. Heller, *J. Amer. Chem. Soc.*, **87**, 731 (1965).

solution of VII in methanol at 20° showed no significant changes within 10 min. Prolonged standing led to rather complex changes which are now being investigated.

**Attempted Condensations of Phospholene III with  $\alpha,\beta$ -Unsaturated Ketones.**—The following unsaturated ketones, methyl vinyl ketone, methyl propenyl ketone, cyclohexenone, and 3-benzylidene-2,4-pentanedione, failed to condense with phospholene III within 5 days at 20 or 60°. Higher temperatures could not be employed since the phospholene itself begins to decompose at an appreciable rate at 100°.

These reactions were carried out under the usual laboratory illuminations. The results of studies of photoinitiated reactions between the phospholene and the unsaturated carbonyl compound will be described elsewhere.<sup>11</sup>

**Hydrolysis of Pentaoxyphosphorane VII with 1 Mol Equiv of Water.**—The hydrolysis of pentaoxyphosphorane VII was studied in  $\text{CHCl}_3$  and in  $\text{CDCl}_3$  using 1 mol equiv of water and of  $\text{D}_2\text{O}$ , respectively. The course of the reaction was followed by  $^1\text{H}$  and  $^{31}\text{P}$  nmr spectrometry. The first product formed was a five-membered cyclic phospho triester, Xa and Xb, together with 2 mol equiv of methanol. The cyclic triester was obtained as two diastereomers at phosphorus, Xa and Xb, in unequal proportions. The configuration at phosphorus was not known with certainty, but, for reasons indicated below, the isomer with the  $^{31}\text{P}$  nmr shift at -14.7 ppm was regarded as having the acetyl group *cis* to the phosphoryl oxygen as in formula Xa.



The  $^1\text{H}$  nmr signals of the cyclic phospho triesters, Xa and Xb, are listed in Table II. The acetyl signal at the lower magnetic field ( $\tau$  7.70) is attributed to the diastereomer Xa with the *cis* relationship of the acetyl and the phosphoryl oxygen. The acetyl signal at higher magnetic field ( $\tau$  7.75) would correspond then to the diastereomer Xb with the *trans*- $\text{CH}_3\text{CO}/\text{O}$ . The acetyl signals of the corresponding diastereomers, Va and Vb, in the propionaldehyde series<sup>6</sup> were at  $\tau$  7.66 and 7.72, respectively.

(11) While this work was in progress, two preliminary communications dealing with photochemical reactions of the phospholene III have appeared: (a) W. G. Bentrude, *Chem. Commun.*, 174 (1967); (b) W. G. Bentrude and K. R. Darnall, *Tetrahedron Lett.*, 2511 (1967).

TABLE II  
<sup>1</sup>H NMR DATA FOR THE OPEN β-PHOSPHO TRIESTER, XII,  
 AND THE 5-CYCLIC PHOSPHO TRIESTERS, Xa AND Xb

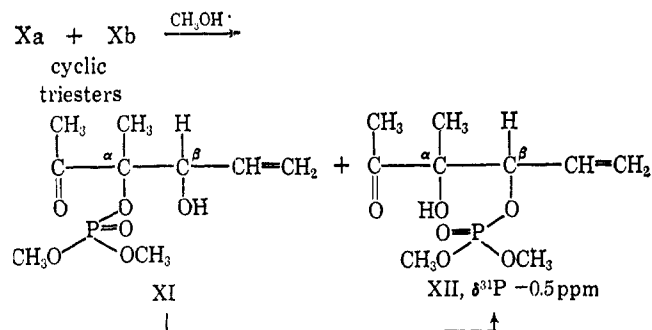
Open triester			Cyclic triester <sup>b</sup>			Assignment
τ <sup>a</sup> of <sup>1</sup> H	No.	J <sup>a</sup>	τ of <sup>1</sup> H	No.	J <sup>a</sup>	
8.63	3	...	8.43	3	...	CH <sub>3</sub> C
			8.33			
7.74	3	...	7.70	3	...	CH <sub>3</sub> CO
			7.75			
6.26 <sup>c</sup>	3	J <sub>HP</sub> = 10.5	6.10 <sup>d</sup>	3	J <sub>HP</sub> = 11.5	CH <sub>3</sub> O
6.20 <sup>c</sup>	3	J <sub>HP</sub> = 11.0	6.08 <sup>d</sup>	3	J <sub>HP</sub> = 11.5	
5.20	1	J <sub>HP</sub> = 8.0 J <sub>HH</sub> = 6.0	5.1	1	...	Methine
4.4	3	Multiplet	4.5	3	Multiplet	Vinyl

<sup>a</sup> τ values in parts per million vs. TMS = 10; J in cycles per second. <sup>b</sup> Two diastereomers at phosphorus. <sup>c</sup> Two magnetically nonequivalent CH<sub>3</sub>O on P. <sup>d</sup> Methoxy of diastereomers at phosphorus.

The signal at τ 8.43 is attributed to the methyl group attached to the phospholane ring in the *cis* isomer Xa, while the signal at τ 8.33 is attributed to the methyl group in the *trans* isomer, Xb. The corresponding signals due to the methyl groups of the *cis* and *trans* isomers, Va and Vb, in the propionaldehyde series were at τ 8.50 and 8.40, respectively. The arguments in favor of the probable configurational assignments to the cyclic phosphates in the propionaldehyde case have already been discussed.<sup>6</sup>

The methanol formed in the hydrolysis of pentaoxyphosphorane VII by 1 mol equiv of water reacted very rapidly with the 5-cyclic phospho triesters, Xa and Xb. The product of this alcoholysis was the open-chain phospho triester, XII, derived from a γ-unsaturated α,β-dihydroxy ketone having the phosphoryl group on the hydroxyl situated at the β carbon.

The <sup>31</sup>P nmr signal showed a coupling with the methine proton on the β carbon in addition to the coupling with the six protons of the two methoxy groups attached to the phosphorus. If the phosphoryl group had been on the α-hydroxy group as in XI, the phosphorus nucleus would have been coupled only with the protons of the methoxy groups.

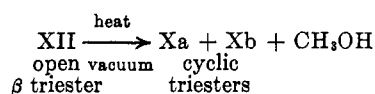


For reasons discussed below, it is very probable that the α-phospho triester XI was the kinetically favored product of the methanolysis of the cyclic triester, X. The α-phosphate, XI, then underwent a rapid rearrangement to the β-phosphate, XII.

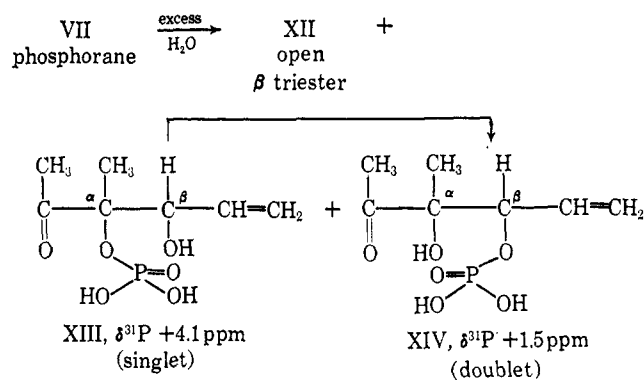
The first observations of the <sup>1</sup>H and <sup>31</sup>P nmr spectra of the hydrolysis product of pentaoxyphosphorane,

VII, were made within 5 min. At this point, the two diastereomeric cyclic triesters, Xa and Xb, and the open β triester, XII, were present in an 80:20 proportion, respectively. This proportion had changed to 20:80 within 20 min and to 5:95 after 45 min. This illustrates the extraordinarily rapid rate of methanolysis of the 5-cyclic phospho triester, X, in solvents of low polarity, like CHCl<sub>3</sub>.

The open β triester, XII, was isolated after the methanolysis of the cyclic triester, X, had reached completion. When the open triester, XII, was distilled under vacuum, it lost one molecule of methanol and gave the two diastereomeric cyclic triesters, Xa and Xb.



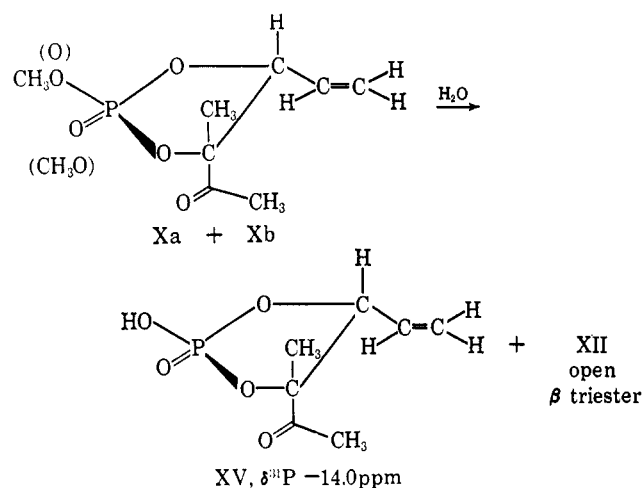
**Hydrolysis of Pentaoxyphosphorane VII with an Excess of Water.**—Extensive hydrolysis occurred very rapidly when 3 mol equiv of water was added to the solution of pentaoxyphosphorane VII in methylene chloride at 20°. The hydrolysis was instantaneous and exothermic when phosphorane VII was added to an excess of water at 0°. This hydrolysis gave three products. The minor product was the same open β triester, XII, previously described; this material was formed in approximately 20–25% yield. The other two products were the phospho monoesters, XIII and XIV, derived from the γ-unsaturated α,β-dihydroxy ketone, having the phosphoryl groups at the α- and β-hydroxy positions, respectively. Both structural isomers could be observed and it was possible to follow the isomerization of the α monoester, XIII, into the β monoester, XIV.



The phosphorus of the α monoester, XIII, gave a singlet while the phosphorus of the β monoester, XIV, gave a doublet, owing to coupling of the phosphorus with the methine protons on the β carbon. The signals for the acetyl and the methyl groups of the α monoester, XIII, were at τ 7.65 and 8.35, respectively. The corresponding signals for the β monoester, XIV, were at τ 7.70 and 8.50, respectively.

**Hydrolysis of the Five-Membered Cyclic Phospho Triesters, Xa and Xb. A. With 1 Mol Equiv of H<sub>2</sub>O in CHCl<sub>3</sub> Solution.**—Under these conditions, the 5-cyclic triesters, Xa and Xb, were converted into two types of phosphates in about equal amounts. One of these was the 5-cyclic diester, XV, which was characterized by the large negative <sup>31</sup>P nmr shift,<sup>6</sup>

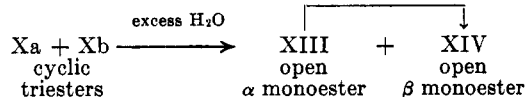
-14.0 ppm. The second product of the hydrolysis was the same open  $\beta$  triester, XII, previously dis-



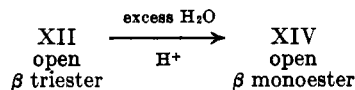
cussed. This remarkable observation suggested that the 5-cyclic triester, X, underwent hydrolysis to the cyclic diester, XV, and 1 equiv of methanol; the methanol then reacted with the remaining cyclic triester giving the open  $\beta$  triester, XII, as before.

**B. With 2 Mol Equiv of  $\text{D}_2\text{O}$  in  $\text{CDCl}_3$  Solution.**—The hydrolysis was followed by means of  $^1\text{H}$  nmr spectrometry and it was shown that after 1 hr at  $20^\circ$  the products were the  $\alpha$ - and the  $\beta$ -phospho monoesters, XIII and XIV. Under these conditions, little or no  $\beta$  triester, XII, was produced; the cyclic diester, XV, underwent further hydrolysis to the open monoesters, XIII and XIV.

**C. With a Large Excess of Water.**—Under these conditions, the formation of the  $\alpha$  and the  $\beta$  monoesters, XIII and XIV, was observed within 5 min. The complete conversion of the  $\alpha$  into the  $\beta$  monoester was observed after 80 min.



**Attempted Hydrolyses of the Open  $\beta$ -Phospho Triester, XII, and the  $\beta$ -Phospho Monoester, XIV.**—The open phospho triester, XII, was relatively stable toward water in  $\text{CHCl}_3$  solution or in an excess of water under neutral conditions at  $20^\circ$ . The addition of acid led to hydrolysis to the  $\beta$ -phospho monoester, XIV. However, no conditions could be found for the complete removal of the phosphorus from the  $\beta$  monoester, XIV, while retaining intact the structure of the sensitive unsaturated dihydroxy ketone.



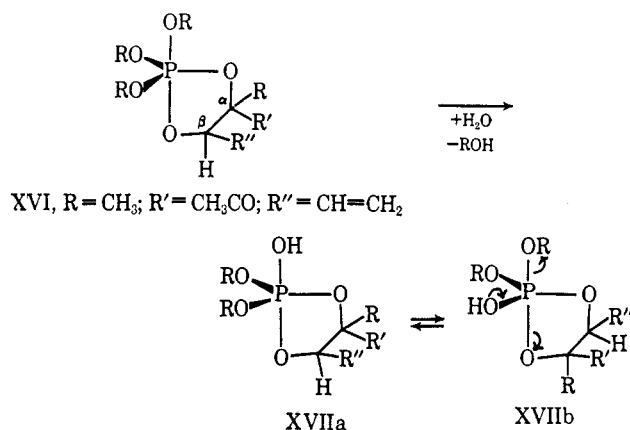
### Discussion

This work showed that derivatives of the 2,2-dihydro-1,3,2-dioxaphospholenes,<sup>4</sup> I, performed a 1,2 addition to the carbonyl group rather than a 1,4 addition to the olefinic double bond of  $\alpha,\beta$ -unsaturated aldehydes. Very mild hydrolyses of the pentaoxyphosphoranes prepared in this manner provided cyclic phospho triesters, Xa and Xb, open phospho triesters,

XI and XII, and phospho monoesters, XIII and XIV, derived from  $\gamma$ -unsaturated  $\alpha,\beta$ -dihydroxy ketones.

It was possible to demonstrate experimentally that a phosphate ester adjacent to a carbonyl function as in XI and XIII was a less stable system than a phosphate ester on a  $\beta$  carbon of the  $\alpha,\beta$ -dihydroxy ketone, as in XII and XIV. Apparently, the migration of the neutral dimethoxyphosphoryl group of the triesters from the  $\alpha$  to the  $\beta$  positions (XI  $\rightarrow$  XII) was considerably faster than the corresponding migration of a dihydroxyphosphoryl group in the monoesters (XIII  $\rightarrow$  XIV).

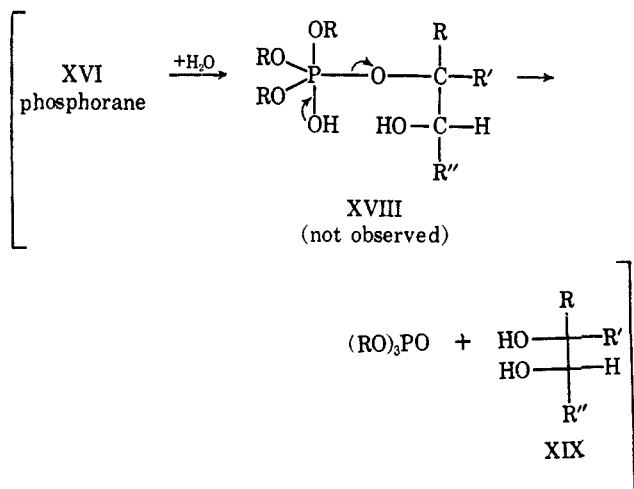
The following interpretation accounts for the observations made during the hydrolyses and the methanolysis of the 5-cyclic pentaoxyphosphoranes and phosphate esters.<sup>12</sup> The first step in the hydrolysis of phosphorane XVI with 1 mol equiv of water is a nucleophilic substitution of the methoxy group by a hydroxy group to form a cyclic hydroxytetraalkoxyphosphorane, XVIIa. Little is known about the mechanism and in particular the stereochemistry, of this substitution.<sup>13a</sup> The available evidence tends to exclude an ionization or  $\text{S}_{\text{N}}1$  mechanism. In this substitution, the longer and probably weaker apical methoxy group is replaced first, but the very rapid positional exchange which results from pseudo-rotation<sup>8-10,12</sup> can lead to other forms of the trigonal bipyramid, for example XVIIb.



If the first substitution on phosphorane XVI had occurred with ring opening to XVIII, the final product would have been trimethyl phosphate and the unsaturated dihydroxy ketone, XIX, since the latter should be more acidic than methanol and, hence, it would be a better leaving group. The retention of the ring during the hydrolysis is an interesting and, apparently, a general phenomenon;<sup>5,6,12</sup> it is, perhaps, related to differences in the strain which may develop

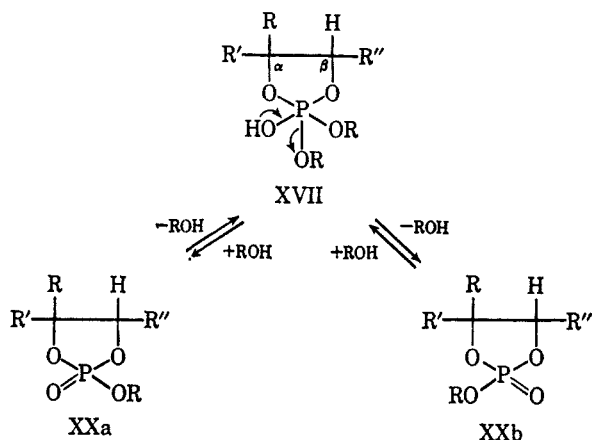
(12) D. Swank, C. N. Caughlan, F. Ramirez, O. P. Madan, and C. P. Smith, *J. Amer. Chem. Soc.*, **89**, 6503 (1967).

(13) (a) For a comprehensive discussion of the stereochemistry of the reactions of organic phosphorus compounds in general, see W. E. McEwen in "Topics in Phosphorus Chemistry," M. Grayson and E. J. Griffith, Ed., Vol. 2, Interscience Publishers, Inc., New York, N. Y., 1965, pp 1-42. (b) NOTE ADDED IN PROOF.—The retention of the ring in the hydrolysis of the cyclic oxyphosphorane is reasonable if the transition state of the hydrolysis resembles the reactant, i.e., a trigonal bipyramid. The latter is more stable when two of the groups are held together in a ring than when all the groups are free to interfere with each other. Therefore, the transition state which results in ring retention should be of lower energy than that which results in ring opening. (c) NOTE ADDED IN PROOF.—The retention of the ring in the collapse of oxyphosphorane to phosphate is also reasonable if the transition state resembles the reactant, i.e., a trigonal bipyramid. This assumption is reasonable since the reaction is highly exothermic.

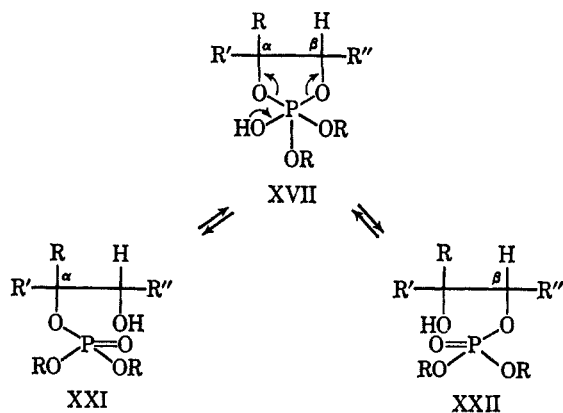


in the transition states leading to ring rupture and to ejection of the methoxy group.<sup>13b</sup>

The cyclic hydroxyphosphorane XVII collapses to the five-membered cyclic triesters XXa + XXb which are stereomers at phosphorus.<sup>13c</sup> Rapid stereomutation among these isomers involves, simply, the readdition of methanol to the phosphoryl group to give the common intermediate XVII.



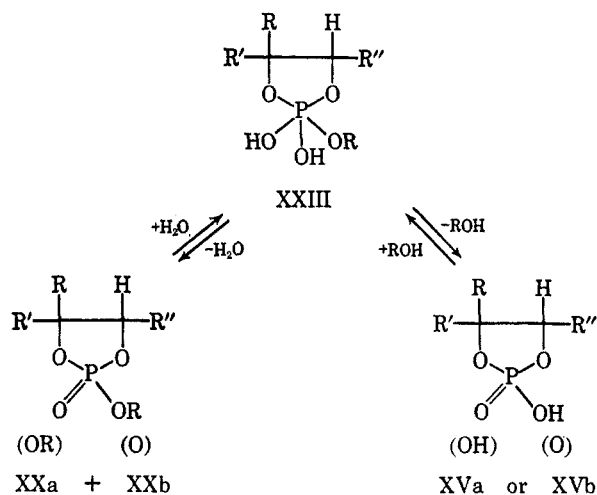
The collapse of hydroxyphosphorane XVII to the  $\alpha$ - and the  $\beta$ -phospho triesters, XXI and XXII, eventually occurs.



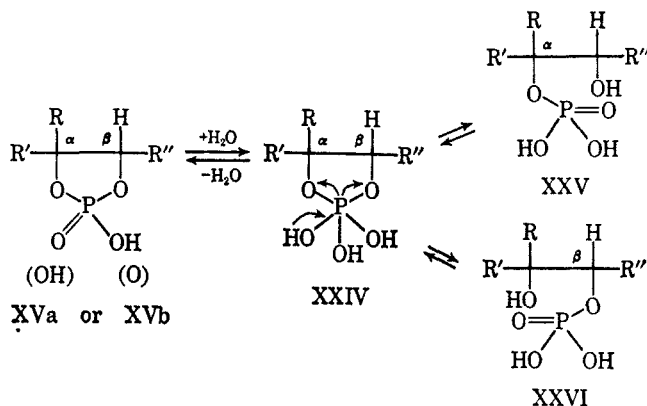
In this picture, the rapid isomerization of the  $\alpha$  into the  $\beta$  triesters, XXI  $\rightarrow$  XXII, proceeds through the common intermediate, XVII. Likewise, the rapid methanolysis of the cyclic triesters, XXa and XXb, proceeds through the common intermediate XVII, leading to the open triesters, XXI and XXII. The

cyclization of the open triester, XXII  $\rightarrow$  XXa + XXb, involves also the same intermediate, XVII.

The hydrolysis of the cyclic triesters, XXa and XXb, probably involves the addition of water to the phosphoryl group, giving the cyclic dihydroxytrialkoxyposphorane XXIII which collapses to the cyclic phospho diester, XVa or XVb, plus methanol.<sup>12,14</sup> The results of these experiments suggest that the addition of methanol to the cyclic triesters, XXa and XXb, to form XVII is as fast as, or faster than, the addition of water to the same triesters XXa and XXb to give XXIII.



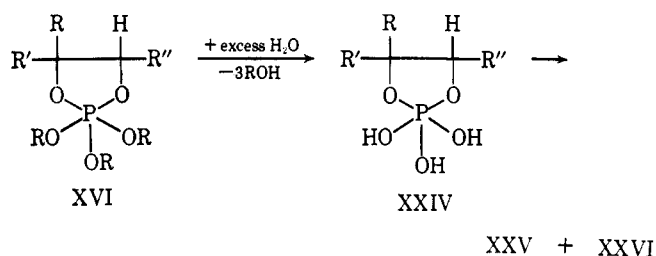
Addition of more water to the cyclic diester XVa or XVb would give the cyclic trihydroxydialkoxyposphorane, XXIV. The latter should collapse to the  $\alpha$  and the  $\beta$  monoesters, XXV and XXVI. The isomerization of the former into the latter proceeds via the cyclic intermediate XXIV.



The formation of the  $\alpha$  and the  $\beta$  monoesters, XXV and XXVI, from the hydrolysis of pentaalkoxyphosphorane XVI with an excess of water could occur by the sequence of reactions just discussed. However, a direct path exists from XVI to the trihydroxyphosphorane, XXIV. It is significant that no open-chain phospho diester was observed; this tends to favor the direct mechanism XVI  $\rightarrow$  XXIV  $\rightarrow$  XXV + XXVI when excess of water is used.<sup>15</sup>

(14) F. Ramirez, O. P. Madan, N. B. Desai, S. Meyerson, and E. M. Banas, *J. Amer. Chem. Soc.*, **85**, 2681 (1963).

(15) This conclusion assumes that the hydrolysis of the open phospho diester to the open phospho monoester is a relatively slow process. There is no evidence for the addition of water to the phosphoryl group of the open-chain phosphate esters.



An important feature of these mechanisms is the ability of water and of methanol to add to the phosphoryl group of a five-membered cyclic phosphate, XXa, XXb, XVa, XVb. There is no evidence that this can happen to open-chain phosphate esters. The difference is probably due to (1) the lower stability of a 5-cyclic phosphate *vs.* an open-chain phosphate<sup>16</sup> and (2) the higher stability<sup>7</sup> of a 5-cyclic oxyphosphorane *vs.* the open-chain analogs.<sup>17</sup>

Much attention<sup>12,14,16,18-21</sup> has been devoted to the mechanism of hydrolysis of 5-cyclic phosphates.<sup>18</sup> Much of the progress in this field is due to the work of Westheimer and his coworkers.<sup>16,19</sup> We first observed the complete retention of the ring when 1 mol of water was added to several 5-cyclic phospho triesters.<sup>14</sup> We related the hydrolysis of the isolated, stable, five-membered cyclic pentaoxyphosphoranes to the hydrolysis of the five-membered cyclic phospho triesters by means of the analogous hypothetical intermediates XXIII and XVII.<sup>5,12,14</sup>

### Experimental Section

Analyses were by Schwarzkopf Microanalytical Laboratories, Woodside, N. Y.

**Reaction of 2,2,2-Trimethoxy-4,5-dimethyl-2,2-dihydro-1,3,2-dioxaphospholene (III) with Acrolein.**—Acrolein (31.2 g, 0.555 mol) was rapidly added to a solution of 90.0 g (0.428 mol) of phospholene III in 400 ml of dry  $\text{CH}_2\text{Cl}_2$  at  $0^\circ$  with stirring. Stirring was continued for 2 hr at  $0^\circ$  and then for 2 days at  $20^\circ$ . Solvent and excess acrolein were evaporated at  $30^\circ$  (20 mm). Distillation at 0.2-mm pressure afforded 102 g (90%) of a clear oil, formulated as 2,2,2-trimethoxy-4 $\beta$ -methyl-4 $\alpha$ -acetyl-5 $\alpha$ -vinyl-2,2-dihydro-1,3,2-dioxaphospholane (VII): bp  $96^\circ$  (0.2 mm);  $n_D^{25}$  1.4501.

*Anal.* Calcd for  $\text{C}_{10}\text{H}_{16}\text{O}_6\text{P}$ : C, 45.0; H, 7.2; P, 11.6. Found: C, 44.9; H, 7.0; P, 11.4.

The  $^1\text{H}$  nmr signals are given in Table I. The infrared spectrum had characteristic bands (in  $\text{CCl}_4$ ) at 5.86 (acetyl) and  $9.39 \mu$  ( $\text{POCH}_3$ ).

**Reaction of the Trimethoxy Biacetylacrolein Phosphite Adduct, VII, with 1 Mol Equiv of Water.**—Water (1 mol equiv, 1.98 ml) was added to a solution containing 28.7 g (0.108 mol)

(16) The extensive work of Westheimer and his coworkers has provided evidence for this strain: (a) J. Kumamoto and F. H. Westheimer, *J. Amer. Chem. Soc.*, **77**, 2515 (1955); (b) J. Kumamoto, J. R. Cox, Jr., and F. H. Westheimer, *ibid.*, **78**, 4858 (1956); (c) P. C. Haake and F. H. Westheimer, *ibid.*, **83**, 1102 (1961); (d) M. Panar, E. T. Kaiser, and F. H. Westheimer, *ibid.*, **85**, 602 (1963); (e) A. Eberhard and F. H. Westheimer, *ibid.*, **87**, 253 (1965); (f) D. A. Usher, E. A. Dennis, and F. H. Westheimer, *ibid.*, **87**, 2320 (1965).

(17) Noncyclic pentaalkoxyphosphoranes have been obtained in solutions from the reactions of dialkyl peroxides with trialkyl phosphites. These phosphoranes appeared to have a low degree of stability: *cf.* (a) D. B. Denney and S. T. D. Gough, *ibid.*, **87**, 138 (1965); (b) D. B. Denney and L. Saferstein, *ibid.*, **88**, 1839 (1966).

(18) For recent summaries with bibliographies, see (a) H. Khorana, "Some Recent Developments on the Chemistry of Phosphate Esters of Biological Interest," John Wiley and Sons, Inc., New York, N. Y., 1961, Chapter 3; (b) A. Todd, *Proc. Chem. Soc.*, 199 (1962).

(19) E. A. Dennis and F. H. Westheimer, *J. Amer. Chem. Soc.*, **88**, 3431, 3432 (1966).

(20) (a) G. Aksnes and K. Bergesen, *Acta Chem. Scand.*, **19**, 931 (1965); (b) *ibid.*, **20**, 2508 (1966).

(21) R. L. Collin, *J. Amer. Chem. Soc.*, **88**, 3281 (1966).

of phospholane VII in 50 ml of chloroform at  $0^\circ$ . The mixture was stirred for 2 hr at  $20^\circ$  and was concentrated at  $20^\circ$  (20 mm). The residue was shown to contain only one type of phosphorus nucleus by  $^{31}\text{P}$  nmr spectroscopy. This substance, which was obtained in nearly quantitative yield, was formulated as 4-methyl-1-hexene-3,4-diol-5-one 3-dimethyl phosphate (XII). The  $^1\text{H}$  nmr spectrum of the pure liquid is summarized in Table II.

The infrared spectrum in  $\text{CCl}_4$  had characteristic bands at  $3.03 \mu$  (OH),  $5.87 \mu$  ( $\text{C}=\text{O}$ ),  $7.92 \mu$  (open-chain phosphate ester), and  $9.60 \mu$  ( $\text{POCH}_3$ ). Attempts to purify this ester by distillation resulted in loss of methanol as described in the next experiment.

**Cyclization of the Open-Chain Phospho Triester to the Corresponding Five-Membered Cyclic Triester.**—A sample (26 g, 0.10 mol) of 4-methyl-1-hexene-3,4-diol-5-one 3-dimethyl phosphate (XII), described in the previous experiment, was submitted to three successive distillations through a 10-cm Vigreux column at 0.2 mm. Methanol (3 ml, 1 mol equiv) was collected in a trap cooled to  $-70^\circ$ . The distillate (21 g, 84% yield) consisted of two diastereomers at phosphorus of 2-methoxy-2-oxo-4 $\beta$ -methyl-4 $\alpha$ -acetyl-5 $\alpha$ -vinyl-2,2-dihydro-1,3,2-dioxaphospholane (Xa + Xb), bp  $116^\circ$  (0.2 mm).

*Anal.* Calcd for  $\text{C}_8\text{H}_{12}\text{O}_5\text{P}$ : C, 43.5; H, 6.0; P, 14.1. Found: C, 43.3; H, 6.1; P, 13.9.

The  $^1\text{H}$  nmr signals are given in Table II. The infrared spectrum in  $\text{CCl}_4$  had characteristic bands at  $5.85 \mu$  ( $\text{C}=\text{O}$ ),  $7.68 \mu$  (cyclic phosphate ester, sharp and strong), and  $9.50 \mu$  ( $\text{POCH}_3$ ).

**Reaction of the 5-Cyclic Phospho Triester (Two Diastereomers at Phosphorus, Xa and Xb) with Methanol.** A.—Methanol (2 mol equiv) was added to a methylene chloride solution of the 5-cyclic phospho triesters at  $20^\circ$  in an nmr sample tube.

B.—An excess of methanol was added to the cyclic triester in the absence of additional solvent. Measurements of the nmr spectra of these solutions were made at various intervals. The only product observed was the open-chain phospho triester XII which was formed at approximately the same rate in both experiments A and B. The pertinent nmr signals are given in Table II.

**Course of the Hydrolysis of the Trimethyl Biacetylacrolein Phosphite Adduct, VII, by 1 Mol Equiv of  $\text{D}_2\text{O}$  in  $\text{CDCl}_3$  Solution by  $^1\text{H}$  Nmr Spectrometry.**—The liquid adduct, VII, was diluted with an equal volume of  $\text{CDCl}_3$  in an nmr sample tube. Deuterium oxide (1 mol equiv) was introduced and the mixture was shaken well for 3 min. The  $^1\text{H}$  nmr spectra were examined at 5-min intervals with the following results: after 5 min, 80% 5-cyclic phospho triester (Xa + Xb), 20% open phospho triester (XII); after 20 min, 20% 5-cyclic phospho triester (Xa + Xb), 80% open phospho triester (XII); after 40 min, 5% 5-cyclic phospho triester (Xa + Xb), 95% open phospho triester (XII).

The  $^{31}\text{P}$  nmr spectra, examined after 5, 15, and 45 min, showed the following: after 5 min, two peaks, cyclic phospho triester and open phospho triester in a ratio of about 80:20; after 15 min, two peaks, cyclic phospho triester and open phospho triester in a ratio of about 50:50; after 45 min, two peaks, cyclic phospho triester and open phospho triester in a ratio of about 5:95.

**Reaction of the Trimethyl Biacetylacrolein Phosphite Adduct, VII, with an Excess of Water.** A.—Adduct VII (56.0 g) was added to 150 ml of water at  $0^\circ$  with stirring. An exothermic reaction was observed. The solution was kept 45 min at  $20^\circ$  and was then titrated with 2 N NaOH to pH 7. Sodium hydroxide (2 mol equiv) was used in the titration to pH 7, which is consistent with the presence of a dibasic acid. This solution was extracted five times, each with 100 ml of  $\text{CHCl}_3$ . The  $\text{CHCl}_3$  layer was evaporated at  $20^\circ$  (20 mm). The residue (23% yield) was identified as 4-methyl-1-hexene-3,4-diol-5-one 3-dimethyl phosphate (XII). The water layer was evaporated to dryness at  $35^\circ$  (0.2 mm). The residue (65% yield, mp  $158-160^\circ$ ) was identified as the disodium salt of 4-methyl-1-hexene-3,4-diol-5-one 3-dihydrogen phosphate (salt of XIV):  $\delta^1\text{P}$  +1.5 ppm ( $\text{D}_2\text{O}$ ).

The  $^1\text{H}$  nmr spectrum in  $\text{D}_2\text{O}$  had the following signals: a singlet at  $\tau$  8.50 (3  $^1\text{H}$ ,  $\text{CH}_3\text{C}$ ), a singlet at 7.70 (3  $^1\text{H}$ ,  $\text{CH}_2\text{CO}$ ), a doublet of doublets at 5.31 with  $J_{\text{HP}} = 8.5$  cps and  $J_{\text{HH}} = 6.2$  cps (1  $^1\text{H}$ , methine), and the vinyl protons, unresolved, centered at 4.25 (3  $^1\text{H}$ ).

B.—The adduct, VII, 3 g, was added to 3 ml of water at  $20^\circ$ . After 10 min, the solution was extracted five times, each with 20 ml of  $\text{CHCl}_3$ , to remove the neutral phospho triester. The

aqueous solution containing the dibasic phospho monoesters (XIII and XIV) was submitted to  $^{31}\text{P}$  and  $^1\text{H}$  nmr spectrometry at several time intervals. After 20 min, two phosphorus nuclei were found: a singlet at +4.1 ppm (phosphate  $\alpha$  to carbonyl as in XIII) and a doublet at +1.5 ppm (phosphate  $\beta$  to carbonyl as in XIV, signal split by the methine proton).

The  $^1\text{H}$  nmr spectrum of the same solution showed singlets at  $\tau$  8.35 ( $\text{CH}_3\text{C}$ ) and 7.65 ( $\text{CH}_3\text{CO}$ ) due to the  $\alpha$ -phospho monoester (XIII) and singlets at  $\tau$  8.50 ( $\text{CH}_3\text{C}$ ) and 7.70 ( $\text{CH}_3\text{CO}$ ) due to the  $\beta$ -phospho monoester (XIV). The structural isomers were present in about equal proportions.

After 2 hr, the  $^{31}\text{P}$  nmr signal of  $\alpha$ -phospho monoester XIII (+4.1 ppm) had disappeared almost completely. The doublet due to  $\beta$ -phospho monoester XIV (+1.5 ppm) had doubled its intensity. The  $^1\text{H}$  nmr signals of the  $\alpha$ -phospho monoesters ( $\tau$  8.35 and 7.65) had decreased to about 10% of their original intensities, while the signals due to the  $\beta$ -phospho monoester ( $\tau$  8.50 and 7.70) had increased by about 90%.

**Hydrolyses of the 5-Cyclic Phospho Triesters (Two Diastereomers at Phosphorus, Xa and Xb) with 1 Mol Equiv of Water.**—Water (1 mol equiv) was added to a solution of the cyclic triesters, Xa and Xb (3.1 g, 12 mmol), in 12 ml of  $\text{CHCl}_3$  at  $20^\circ$ . The solvent was removed at  $20^\circ$  and 20 mm, leaving a light brown, oily residue. The  $^{31}\text{P}$  nmr spectrum of this liquid had two signals of about equal intensities. One of them at -0.5 ppm was due to the  $\beta$ -open phospho triester (XII). The other at -14.0 was due to the 5-cyclic phospho diester, XVa or XVb.

The  $^1\text{H}$  nmr signal of the original  $\text{CHCl}_3$  solution confirmed these assignments and showed the absence of methanol; *i.e.*,

the methanol produced in the hydrolysis reacted with the cyclic triester, X, to give the open triester, XII.

**Hydrolyses of the 5-Cyclic Phospho Triesters (Two Diastereomers at Phosphorus, Xa and Xb) with an Excess of Water.**

—The 5-cyclic triesters, Xa and Xb, were mixed with an equal volume of water in an nmr sample tube. After the exothermic reaction had subsided, the solution was analyzed by  $^{31}\text{P}$  and  $^1\text{H}$  nmr spectrometry at various time intervals. The signals due to the  $\alpha$  monoester, XIII (+4.1,  $\tau$  8.35 and 7.65), which were observed after 30 min, had vanished completely after 2.5 hr. The corresponding signals due to the  $\beta$ -phospho monoester, XIV, had increased in intensity. When the solution was heated 3 min at  $100^\circ$ , it turned dark brown and was not investigated further.

**Behavior of the Open-Chain  $\beta$ -Phospho Triester toward Hydrolysis.** A.—The open-chain  $\beta$ -phospho triester, XII, was mixed with an equal volume of water at  $20^\circ$ . The  $^1\text{H}$  nmr spectrum taken at 30-min intervals over a period of 8 hr revealed no significant change.

B.—Addition of 1 drop of phosphoric acid to the aqueous solution caused hydrolysis to the  $\beta$ -phospho monoester (XIV). After 10 min, the extent of the hydrolysis was roughly 5–10%; after 5 hr, approximately 5% of the original signal due to the  $\text{POCH}_3$  group was present. These results were confirmed by  $^{31}\text{P}$  nmr analysis.

**Registry No.**—VII, 15353-05-6; Xa, 15353-06-7; Xb, 15353-07-8; XII, 15353-08-9; disodium salt of XIV, 15353-09-0.

## New Syntheses of $\beta$ -Keto- $\alpha$ -hydroxy Acid Chlorides, of $\alpha$ -Hydroxy $\beta$ -Diketones, and of Their Phosphate Esters

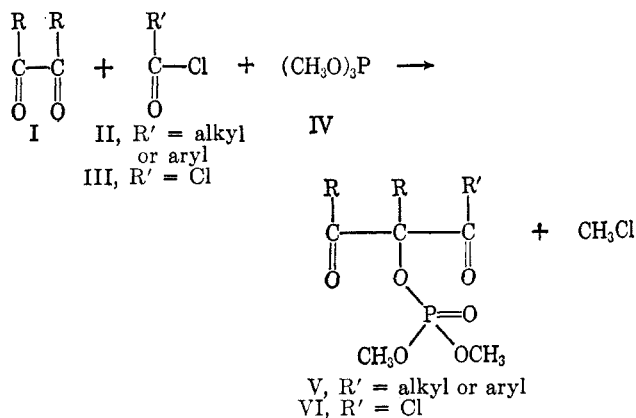
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Received September 28, 1967

The 1:1 adduct made from biacetyl,  $\text{CH}_3\text{COCOCH}_3$ , and trimethyl phosphite,  $(\text{CH}_3\text{O})_3\text{P}$ , namely, 2,2,2-trimethoxy-4,5-dimethyl-2,2-dihydro-1,3,2-dioxaphospholene, performed a nucleophilic substitution at the carbonyl carbon of carboxylic acid chlorides,  $\text{R}'\text{COCl}$ , and of phosgene,  $\text{ClCOCl}$ . This new reaction provided a direct synthesis of phosphate esters derived from  $\alpha$ -hydroxy  $\beta$ -diketones,  $\text{R}'\text{COC}(\text{OH})(\text{R})(\text{COR})$ , and from  $\beta$ -keto- $\alpha$ -hydroxy acid chlorides,  $\text{ClCOC}(\text{OH})(\text{R})(\text{COR})$ . The  $\alpha$ -hydroxy  $\beta$ -diketone phosphates underwent an extraordinarily facile hydrolysis to the diketo alcohols.

This paper describes two related new reactions. In one of them, a trialkyl phosphite, IV, was used as the reagent to effect the carbon-carbon condensation of an  $\alpha$ -diketone, I, with a carboxylic acid chloride, II, to form the phosphate ester, V, of an  $\alpha$ -hydroxy  $\beta$ -diketone. In the second reaction, the trialkyl phosphite, IV, effected the condensation of an  $\alpha$ -diketone, I, with phosgene, III, to form the phosphate ester, VI, of a  $\beta$ -keto  $\alpha$ -hydroxy acid chloride.

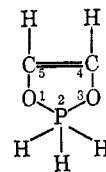


(1) This investigation was supported by Public Health Service Grant No. CA-04769-08 from the National Cancer Institute, and by the National Science Foundation Grant CP-6690-Y.

phite, IV, effected the condensation of an  $\alpha$ -diketone, I, with phosgene, III, to form the phosphate ester, VI, of a  $\beta$ -keto  $\alpha$ -hydroxy acid chloride.

These reactions were carried out in two steps. First, the  $\alpha$ -diketone and the phosphite ester were combined in the form of a 2,2,2-trialkoxy-2,2-dihydro-1,3,2-dioxaphospholene,<sup>2,3</sup> VII. Then the phospholene VII was mixed with the acid chloride II or III to give methyl chloride and the corresponding phosphate ester V or VI. It was assumed<sup>4</sup> that a tetra-

(2) The parent ring system can be named 2,2-dihydro-1,3,2-dioxaphospholene. This name implies the pentacovalency of the phosphorus.



(3) The literature on 2,2-dihydro-1,3,2-dioxaphospholenes has been reviewed: (a) F. Ramirez, *Pure Appl. Chem.*, **9**, 337 (1964); (b) W. C. Hamilton, S. J. LaPlaca, F. Ramirez, and C. P. Smith, *J. Amer. Chem. Soc.*, **89**, 2268 (1967).

(4) (a) F. Ramirez, S. B. Bhatia, and C. P. Smith, *ibid.*, **89**, 3026 (1967); (b) F. Ramirez and N. B. Desai, *ibid.*, **82**, 2652 (1960).