Crystal and Molecular Structure of a Furanose Five-Membered Cyclic Phosphodiester, $[(CH_3)_4(CH_3O)_2C_4O]PO_4H$. Anomeric Carbon to Phosphate Phosphorus Group Translocation in Sugar Phosphates[1]

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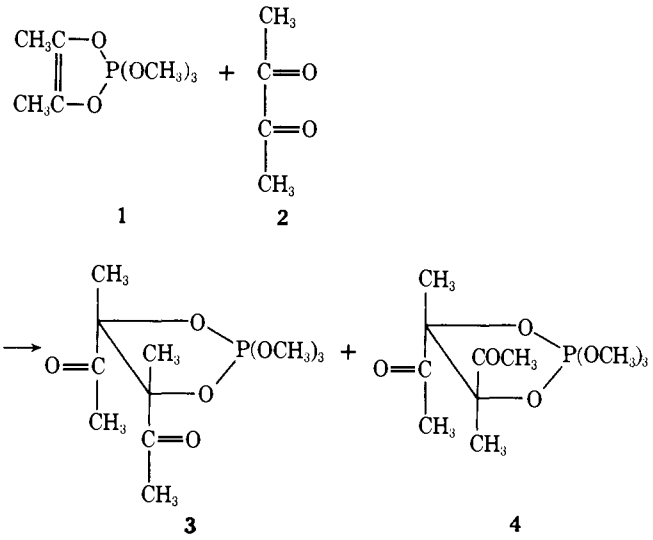
Abstract: The crystal and molecular structure of a furanose five-membered cyclic phosphodiester 2r,3t,4t,5c-tetramethyl-2,5-dimethoxy-3,4-dihydroxytetrahydrofuran-3,4-cyclic hydrogenphosphate, $[(CH_3)_4(CH_3O)_2C_4O]PO_4H$, was solved by x-ray crystallographic techniques. The compound crystallizes in space group $P\bar{1}$ of the triclinic system with two molecules in a cell of dimensions a = 8.284 (2), b = 9.149 (2), c = 9.264 (1) Å, α = 94.54 (2), β = 104.37 (1), γ = 90.26 (2)°. The observed and calculated densities are 1.39 and 1.36 g cm^{-3}, respectively. Data were obtained on a computer-controlled Enraf-Nonius CAD-4 diffractometer. The structure has been refined by full matrix least-squares techniques to a final R factor on F of 6.7% based on 2205 independent reflections. The two fused five-membered rings are puckered, and the molecule lacks a mirror plane. Both rings are irregular pentagons with angles ∠OPO = 98.3, ∠POC > 113, and ∠OCO < 106° in the phosphate, and ∠CCC < 105, ∠OCC < 105, and ∠COC ~ 110° in the furanose. The PO_4 group is a highly distorted tetrahedron. The furanose cyclic phosphodiester was obtained as a result of a group translocation in which a hydroxyl group at the anomeric carbon of the 1,6-dideoxy-α-DL-*lyxo* hexulose derivative, and the methoxy group at the phosphorus atom of its 3,4-cyclic phosphotriester exchange positions spontaneously at 25 °C in acetonitrile solution. The rearrangement is favored by aprotic solvents of relatively high polarity, and is inhibited by tertiary amines. Possible mechanisms are discussed.

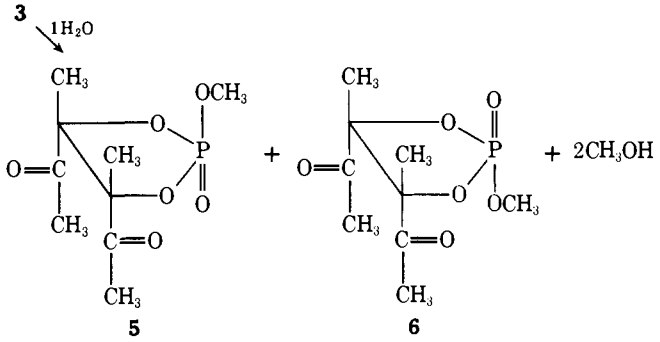
The condensation of 2,2,2-trialkoxy-1,3,2-dioxaphospholenes with carbonyl functions, e.g., **1** + **2** → **3** + **4**, was dis-



covered in 1961.[3-6] Numerous applications of the "dioxaphospholene condensation" have been reported,[7] and its recent utilization in the synthesis of branched sugars has been described by David, Lepine, Aranda, and Vass[8].

This paper deals with an aspect of the hydrolysis of the pentaoxyphosphoranes that are obtained from the dioxaphospholene condensation.[9-11] The complete hydrolysis of the *meso*- and the *rac*-oxyphosphoranes,[12-14] **3** and **4**, affords *meso*- and *rac*-3,4-dimethyl-3,4-dihydroxyhexane-2,5-dione, $CH_3COC(CH_3)(OH)C(CH_3)(OH)COCH_3$. The partial hydrolysis of the *meso*-oxyphosphorane **3** gives two cyclic phosphotriesters, **5** and **6**, which differ in configuration at the phosphorus atom.[9]

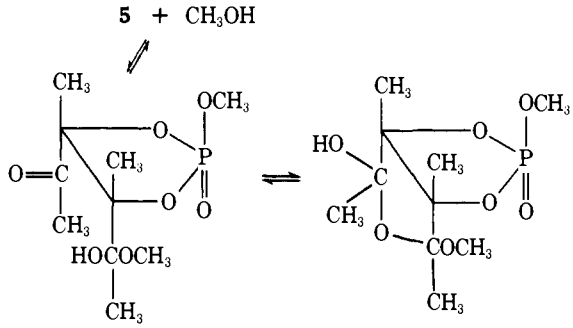
The diketo triesters, **5** and **6**, can be isolated under certain conditions, or the methanol produced in the hydrolysis can be

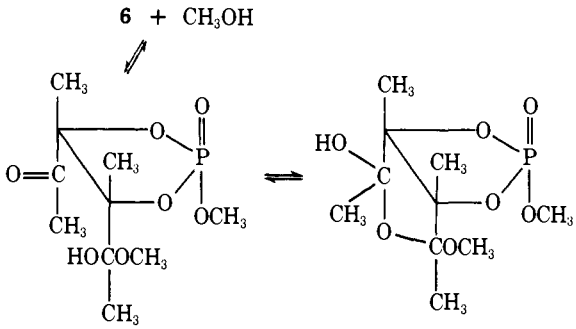


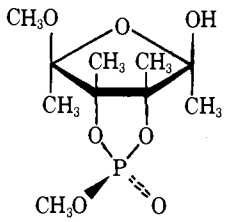
allowed to add to the carbonyl groups present in the triesters. The initial products of this reaction are the *acyclic* hemiketal triesters, **7** and **9**, respectively; the latter are reversibly transformed into the corresponding *cyclic* hemiketal triesters, **8** and **10**.

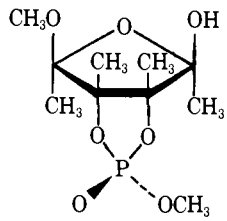
In principle, the hemiketal triester **8** can exist as four diastereomers, each one of them being a pair of enantiomers; one of these enantiomers is depicted in formula **8-I-α**. The same conclusion applies to triester **10**, and the corresponding enantiomer is shown in formula **10-I-α**. These two formulas differ only in the spatial relationship between CH_3O–P and the bridgehead methyl groups: cis in **8-I-α** and trans in **10-I-α** (or, with respect to the bicyclic cage, *exo*- and *endo*-CH_3OP, respectively).

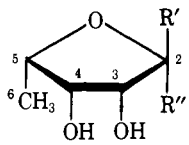
Formulas **8-I-α** and **10-I-α** are derived from 1,6-dideoxy-α-L-*lyxo*-hexulose by appropriate substitutions at C(3), C(4), and C(5) (carbohydrate numbering). The anomers, **8-I-β** and **10-I-β**, are easily visualized by substitutions on 1,6-dideoxy-β-L-*lyxo*-hexulose. The remaining formulas **8-II-α** and **8-II-β**, and **10-II-α** and **10-II-β** are derived by similar substitutions on the α and β anomers of 1,6-dideoxy-D-*ribo*-hexulose. (L-lyxo and D-ribo configurations are depicted for simplicity; the substance prepared in this work is a racemate, i.e., a derivative of the corresponding DL forms).



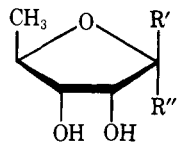






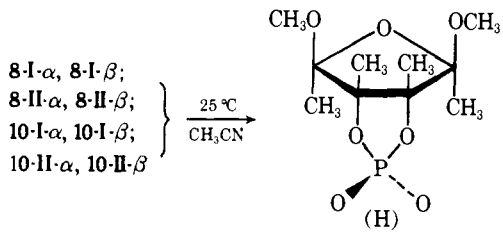


I = lyxo
1,6-Dideoxy-L-*lyxo*-hexulose
α, R′ = OH; R″ = CH_3
β, R′ = CH_3; R″ = OH



II = ribo
1,6-Dideoxy-D-*ribo*-hexulose
β, R′ = OH; R″ = CH_3
α, R′ = CH_3; R″ = OH

Of the eight possible diastereomers of **8** and **10**, only one, of unknown configuration, could be obtained[9] in crystalline form, in about 55% yield, based on oxyphosphorane **3**. A solution of this crystalline substance in acetonitrile underwent a remarkable molecular rearrangement to the cyclic ketal phosphodiester **11**.[15]



The number of diastereomers possible for the ketal diester **11** depends on the placement of the acidic proton; if there is no operational distinction between the two oxygen atoms bonded to the phosphorus, only three diastereomers need to be considered, two meso and one racemic forms. The meso form depicted in **11** is 2r,3t,4t,5c-tetramethyl-2,5-dimethoxy-3,4-dihydroxytetrahydrofuran-3,4-cyclic phosphate. The crystal and molecular structure of this substance has now been established by x-ray analysis and is reported in this paper. A knowledge of the configuration and the conformation of **11** in the crystal should be useful in an analysis of the possible mechanisms of the molecular rearrangement of **8** or **10** in solution.

Experimental Section

***meso*-2,2,2-Trimethoxy-4,5-dimethyl-4,5-diacetyl-2,2-dihydro-1,3,2-dioxaphospholane (3).** The oxyphosphorane **3**, mp 31-32 °C (from pentane), was synthesized from biacetyl (**2**) and trimethyl phosphite via 2,2,2-trimethoxy-4,5-dimethyl-2,2-dihydro-1,3,2-dioxaphospholene (**1**) as previously described;[9] the ^{31}P and ^{1}H NMR data of **3** agreed with those in the literature.

2r,3t,4t,5c-Tetramethyl-5-methoxy-2,3,4-trihydroxytetrahydrofuran-3,4-cyclic Methylphosphate or 3,4-*O,O*-Methoxyphosphoryl-1,6-dideoxy-3,4-di-*C*-methyl-5-*C*-methoxy-α-DL-*lyxo*-hexulose (8-I-α or 10-I-α). (Configuration assigned by analogy to that of the ketal diester, **11**, established by x-ray analysis.) Water (0.59 g; 30 mmol) was added to a stirred solution of the *meso*-oxyphosphorane (**3**; 8.9 g; 30 mmol) in *anhydrous* diethyl ether (30 mL) at 25 °C. Within a few minutes the solution became warm from the heat of reaction. The solution was stirred for 24 h at 25 °C, concentrated to about one-half of its original volume, and kept 12 h at − 10 °C. The resulting crystals were collected, washed with a small volume of anhydrous ether, and dried under vacuum. A second crop was obtained from the filtrate; total yield of **8-I-α** (*exo*-CH_3OP) or **10-I-α** (*endo*-CH_3OP): 4.30 g, or 53% of the theory based on oxyphosphorane **3**. A fresh $CDCl_3$ solution of the crystals, immediately after their preparation, had one signal at $\delta_{^{31}P}$ −13.6 ppm (vs. H_3PO_4 = 0), and signals at $\tau_{^1H}$ (ppm vs. Me_4Si = 10) 8.50, 8.55, 8.58 (1:2:1), 6.65 (1), and 6.15 (1) (doublet, J = 11.5 Hz), in addition to a variable signal due to OH at ca. 5.7. The crystals were sensitive to moisture, and were stored under N_2.

Molecular Rearrangement of Hemiketal Triester 8-I-α or 10-I-α. Isolation of 2r,3t,4t,5c-Tetramethyl-2,5-dimethoxy-3,4-dihydroxytetrahydrofuran-3,4-cyclic Hydrogenphosphate (Ketal Diester 11). A solution of freshly prepared hemiketal triester (**8-I-α** or **10-I-α**; 2.65 g; 9.3 mmol) in *anhydrous* acetonitrile (20 mL) was kept for 24 h at 30 °C. The solution was concentrated to one-half of its original volume, and kept for several days at −10 °C. The resulting crystals (1.23 g) were collected; the filtrate was concentrated somewhat to yield additional crystals (0.4 g). The yield of ketal diester **11**, mp 115-116 °C, was 62% of the theory. A solution of **11** in $CDCl_3$ had $\delta_{^{31}P}$ −16.0 ppm, $\tau_{^1H}$ 8.58 and 6.75 ppm, in addition to a variable signal due to the acidic proton at ca. −2 ppm.

The crystals of **11** for x-ray analysis were grown, slowly, from a ca. 0.7 M acetonitrile solution at 20 °C.

Effect of Solvent and of Base on the Molecular Rearrangement of the Hemiketal Triester (8-I-α or 10-I-α). (a) A 0.2 M CD_3CN solution of **8** (or **10**) was monitored by ^{1}H NMR spectrometry at 25 °C. Approximately one-half of the original compound **8** (or **10**) disappeared in about 12 h, and was transformed into the ketal diester **11**. There were relatively small amounts of by-products formed, according to the NMR spectra.

(b) Diisopropylethylamine (1 mol equiv) was added to a 0.2 M CD_3CN solution of the hemiketal triester **8** (or **10**), and the reaction was monitored by ^{1}H NMR spectrometry. No significant changes were noted in the original spectrum even after 63 h.

(c) The ^{1}H NMR spectra of 0.5 M $CDCl_3$ and 0.5 M CD_3CN solutions of the hemiketal diester **8** (or **10**) were recorded at various time intervals at 25 °C. The spectra in $CDCl_3$ solution became quite complex and continued to change over the course of 11 days. However, the spectral changes in CD_3CN were simple and were consistent with the rearrangement of **8** (or **10**) into **11**.

Crystal Data. $C_{10}H_{19}O_7P$ (**11**): triclinic; $P\bar{1}$; a = 8.284 (2), b = 9.149 (2), c = 9.264 (1) Å; cos α = −0.0792 (3), cos β = −0.2482 (2), cos γ = −0.0046 (3); V = 677.8 (1) Å^3 ($\lambda_{CuK\alpha}$ = 1.5418 Å at 21 °C); Z = 2 (one molecule per asymmetric unit); D_{calcd} = 1.36 g cm^{-3}, D_{meas} (by flotation in *n*-hexane-carbon tetrachloride) = 1.39 (1) g cm^{-3}; μ(Cu Kα) = 20.3 cm^{-1}.

Data Collection and Structure Refinement. Precession photographs and subsequent searching of reciprocal space by automatic diffractometer showed the unit cell to be triclinic and of space group $P\bar{1}$. The

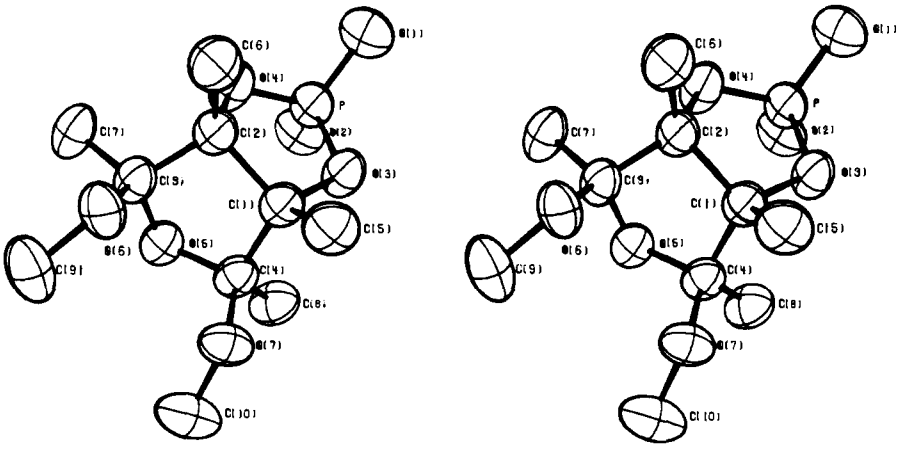


Figure 1. Stereoscopic drawing of an isolated molecule of the cyclic ketal phosphodiester, **11**, $C_{10}H_{19}O_7P$. The 50% probability ellipsoids are shown. (Hydrogen atoms are omitted for clarity.)

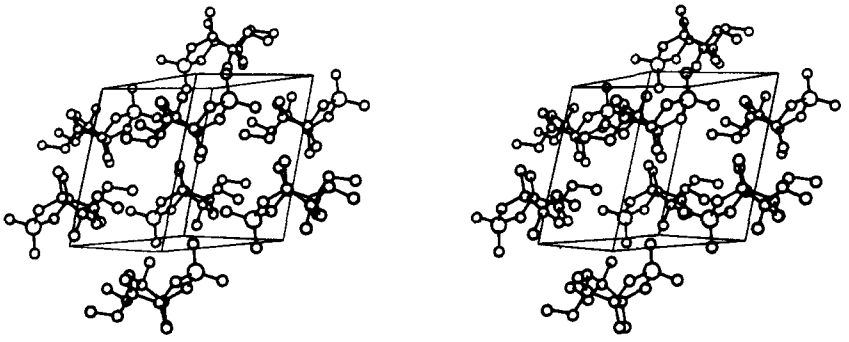


Figure 2. Stereoscopic drawing showing the unit cell contents ($Z = 2$) with all molecules completed; c is approximately vertical.

cell dimensions were determined by a least-squares fit of the observed 2θ angles for 14 reflections centered automatically.

Intensity data were collected from a colorless crystal of approximately triangular prismatic habit and dimensions 0.25 × 0.20 × 0.15 mm. The data crystal was moisture sensitive, and was wedged inside a glass capillary tube, where it remained stable over the course of the data collection. Data were collected on a computer-controlled Enraf-Nonius CAD-4 diffractometer using nickel-filtered Cu Kα radiation, which was monochromatized by reflection from a highly oriented graphite monochromator. Two data sets were collected for 2θ (Cu Kα) < 150°. The 4800 observations gave 2205 independent reflections with $F_0^2 > 3\ \sigma$ count (F_0^2) with $\sigma\ (F_0^2)$ being based on Poisson counting statistics. The intensities of five standard reflections were measured periodically and were found to have fallen off to approximately 85% of their original values by the end of data collection. The decrease in intensity was uniform over the exposure time and the individual standards were scaled to the zero time standards. Data were collected by θ-2θ scans. Normal scans which did not result in sufficiently high precision on net intensity measurements were repeated at a slower scan speed. Background was measured on one-sixth of the total scan width. The takeoff angle was 5.80° and the diffracted beam was automatically corrected for coincidence losses.

Structure factors were derived in the usual way; no absorption correction was made. Normalized structure factors (E's) were used in a multiple solution direct methods technique as described by Germain, Main, and Woolfson[16] to determine phases from which an E map revealed the coordinates of all but one of the nonhydrogen atoms.

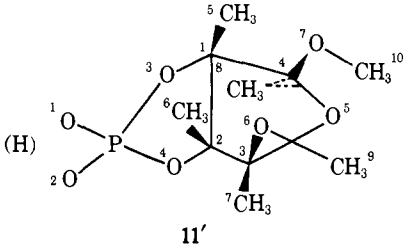
The structure was refined by full matrix least squares, minimizing the function $\Sigma w\Delta^2$ with $\Delta = |F_0| - |F_c|$ with weights $w = 4F_0^2/\sigma^2(F_0)^2$ and $\sigma^2(F_0^2) = \sigma^2$ count $(I) + (0.03F^2)^2$. Hydrogen atom positions (14) were located by difference Fourier synthesis using low-angle ($(\sin\theta)/\lambda < 0.35$) data. Four of the five remaining hydrogen atoms were placed in idealized positions; no attempt was made to place the hydroxyl hydrogen. Atomic scattering factors for all nonhydrogen atoms were taken from a standard source,[17] while that for hydrogen atoms was the best spherically averaged value of Stewart et al.[18]

The final least-squares cycles included anisotropic thermal parameters for the nonhydrogen atoms and individual isotropic thermal parameters on the hydrogen atoms. The final values of $R_1 = \Sigma||F_0| - |F_c||/\Sigma|F_0|$ and $R_2 = \{[w||F_0| - |F_c||^2]/\Sigma wF_0^2\}^{1/2}$ were 0.067 and 0.089, respectively, and the error in an observation of unit weight was 3.68. The maximum density in a final difference electron density synthesis was 0.35 e Å^{-3}, approximately 40% of the height of a hydrogen atom. The final parameters are presented in Tables II and III, and the structure amplitudes as $10|F_0|$ and $10|F_c|$ in Table IV. (See paragraph concerning supplementary material at the end of this paper.)

Discussion of Results

Molecular Structure of the Ketal Phosphodiester 11. Figure 1 shows the structure of an individual molecule, and includes the numbering system for the nonhydrogen atoms and the 50% probability vibrational ellipsoids. Figure 2 depicts the unit cell contents and the packing of the molecules. The interatomic distances, bond angles, and their standard deviations for nonhydrogen atoms are given in Table I and were calculated from the positional parameters listed in Table II and the correlation matrix. The pertinent data concerning hydrogen atoms are given in Table III. Several dihedral angles between planes are shown in Table V, and some relatively short intramolecular nonbonded distances are indicated in Table VI.

The diester **11** has a bicyclo [3.3.0] octane skeleton,[19a] and



11′

Table I. Bond Distances (Å) and Angles (deg)[a,b]

	Distances		
P-O(1)	1.508 (3)	C(9)-O(6)	1.427 (5)
P-O(2)	1.484 (3)	C(10)-O(7)	1.431 (5)
P-O(3)	1.575 (2)	C(1)-C(2)	1.560 (4)
P-O(4)	1.562 (2)	C(1)-C(4)	1.558 (4)
C(1)-O(3)	1.464 (3)	C(2)-C(3)	1.531 (5)
C(2)-O(4)	1.466 (3)	C(1)-C(5)	1.513 (4)
C(3)-O(5)	1.420 (4)	C(2)-C(6)	1.512 (5)
C(4)-O(5)	1.434 (4)	C(3)-C(7)	1.512 (4)
C(3)-O(6)	1.405 (3)	C(4)-C(8)	1.523 (4)
C(4)-O(7)	1.406 (3)		
	Angles		
	In Cyclic Phosphate		
O(1)-P-O(2)	113.4 (1)	O(3)-P-O(4)	98.3 (1)
O(1)-P-O(3)	109.1 (2)	P-O(4)-C(2)	113.8 (2)
O(1)-P-O(4)	110.8 (2)	O(4)-C(2)-C(1)	105.3 (2)
O(2)-P-O(3)	113.2 (2)	C(2)-C(1)-O(3)	104.7 (2)
O(2)-P-O(4)	111.2 (2)	C(1)-O(3)-P	113.6 (2)
	In Furanose Ring		
C(1)-C(2)-C(3)	102.9 (2)	O(5)-C(4)-C(1)	104.6 (2)
C(2)-C(3)-O(5)	103.8 (2)	C(4)-C(1)-C(2)	104.7 (2)
C(3)-O(5)-C(4)	110.0 (2)		
	In Exocyclic Groups		
C(5)-C(1)-O(3)	105.8 (3)	C(8)-C(4)-O(5)	107.2 (2)
C(5)-C(1)-C(2)	115.9 (3)	C(8)-C(4)-C(1)	116.0 (2)
C(5)-C(1)-C(4)	115.5 (3)	C(3)-O(6)-C(9)	115.5 (3)
C(6)-C(2)-O(4)	107.5 (3)	C(4)-O(7)-C(10)	116.1 (3)
C(6)-C(2)-C(1)	117.5 (2)	O(6)-C(3)-O(5)	112.1 (3)
C(6)-C(2)-C(3)	116.3 (3)	O(6)-C(3)-C(2)	104.3 (3)
C(7)-C(3)-O(6)	112.3 (3)	O(7)-C(4)-O(5)	110.7 (2)
C(7)-C(3)-O(5)	108.6 (3)	O(7)-C(4)-C(1)	106.6 (2)
C(7)-C(3)-C(2)	115.6 (3)	O(3)-C(1)-C(4)	109.6 (2)
C(8)-C(4)-O(7)	111.4 (3)	O(4)-C(2)-C(3)	106.4 (3)

[a] Numbers in parentheses here and in succeeding tables are estimated standard deviations in the least significant digits. [b] Bond distances and angles involving hydrogen atoms are included with the supplementary material.

Table II. Positional and Thermal Parameters ($\times 10^4$) for Nonhydrogen Atoms[a]

Atom	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
P	3857 (1)	9075 (1)	1459 (1)	169 (1)	133 (1)	134 (1)	2 (1)	71 (1)	42 (1)
O(1)	5006 (4)	399 (3)	1969 (3)	249 (5)	156 (4)	149 (3)	−34 (3)	83 (3)	22 (3)
O(2)	3612 (4)	8599 (3)	−151 (3)	265 (6)	172 (4)	144 (4)	−34 (4)	76 (4)	39 (3)
O(3)	4488 (3)	7817 (3)	2513 (3)	152 (3)	143 (3)	153 (3)	27 (2)	77 (3)	54 (2)
O(4)	2151 (3)	9340 (3)	1859 (3)	190 (4)	159 (3)	215 (4)	54 (3)	111 (4)	110 (3)
O(5)	672 (3)	6449 (2)	1528 (2)	167 (4)	131 (3)	112 (3)	20 (2)	36 (2)	23 (2)
O(6)	−153 (3)	7150 (3)	3720 (3)	160 (4)	165 (3)	130 (3)	−16 (3)	67 (3)	29 (2)
O(7)	2138 (3)	4854 (2)	3207 (3)	229 (5)	107 (3)	136 (3)	−5 (3)	39 (3)	40 (2)
C(1)	3224 (4)	7265 (3)	3205 (3)	154 (4)	112 (3)	120 (4)	15 (3)	59 (3)	37 (3)
C(2)	1902 (4)	8489 (3)	3065 (4)	156 (4)	112 (3)	138 (4)	16 (3)	74 (3)	42 (3)
C(3)	254 (4)	7629 (4)	2447 (4)	152 (5)	134 (4)	125 (4)	24 (3)	62 (3)	32 (3)
C(4)	2280 (4)	5914 (3)	2224 (3)	167 (5)	114 (3)	115 (3)	22 (3)	47 (3)	30 (3)
C(5)	4142 (5)	6979 (4)	4782 (4)	206 (6)	135 (4)	119 (4)	−1 (4)	28 (4)	40 (3)
C(6)	1996 (5)	9551 (4)	4420 (5)	190 (6)	145 (5)	192 (6)	7 (4)	84 (5)	−17 (4)
C(7)	−1142 (5)	8462 (5)	1510 (5)	175 (6)	189 (6)	175 (5)	71 (5)	51 (5)	52 (5)
C(8)	3038 (6)	5280 (5)	979 (5)	245 (8)	140 (5)	170 (5)	38 (5)	94 (5)	3 (4)
C(9)	−1539 (6)	6143 (7)	3433 (6)	190 (7)	232 (8)	201 (7)	−44 (6)	77 (6)	43 (6)
C(10)	1347 (8)	3489 (5)	2531 (6)	348 (12)	132 (5)	178 (6)	−52 (6)	30 (7)	31 (5)

[a] Anisotropic thermal parameters in the form $\exp[-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + 2\beta_{12}hk + 2\beta_{13}hl + 2\beta_{23}hl)]$.

details of the structure are conveniently discussed with reference to the idealized formula **11′**. The position of the acidic hydrogen has not been assigned, although it may be significant that the two bond distances P-O(1) and P-O(2) differ by an amount which exceeds three standard deviations, suggesting some double bond character in 0(2), i.e., the *endo*-oxygen of the bicyclic system.

A noteworthy feature of the structure is the presence of three butane chains, C(5)-C(1)-C(2)-C(6), C(5)-C(1)-C(4)-C(8), and C(6)-C(2)-C(3)-C(7), which are forced to adopt eclipsed, or at best slightly skewed, conformations by the bicyclic skeleton, although these eclipsings involve two methyl groups, C(5) and C(6), and two tetrasubstituted carbons, C(3) and C(4).

The planes containing atoms P, O(1), O(2) and P, O(3), O(4) are nearly orthogonal, with a dihedral angle of 88.6 (2)°; however, there is no mirror plane bisecting the molecule across O(1), P, O(2), O(5), and the midpoint of bond C(1)-C(2).

Table V. Some Dihedral Angles Between Planes

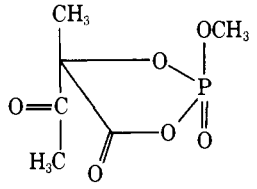
Plane no.	Atoms in plane	Plane no.	Atoms in plane	Dihedral angle, deg
1	O(3), C(1), C(2)	2	O(4), C(2), C(1)	18.6 (3)
3	C(4), C(1), C(2)	4	C(3), C(2), C(1)	21.0 (3)
4	C(1), C(2), C(3)	5	O(5), C(3), C(2)	30.5 (3)
3	C(2), C(1), C(4)	6	O(5), C(4), C(1)	5.1 (3)

Both rings are puckered. The torsional angle about bond C(1)-C(2) is 18.6° in the phosphate and 21.0° in the furanose, as defined, respectively, by the corresponding dihedral angles listed in Table V. There is significant torsion (30.5°) about bond C(2)-C(3), but little (5.1°) about C(1)-C(4), as given by the respective dihedral angles.

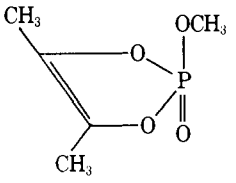
The data suggest the presence of considerable torsion, steric, and angle strain in the molecule of **11**. The steric strain arises mainly from repulsions between the two adjacent *cis*-methyl groups, C(5) and C(6), and between those methyl groups and the respective adjacent *cis*-methoxy groups, O(7) and O(6). The estimated van der Waals radii for the methyl group and the oxygen atom are 2.0 and 1.4 Å, respectively.[19b] The observed intramolecular nonbonded distances given in Table VI are significantly shorter than the sums of these hypothetical van der Waals radii: 2.95 Å vs. the calculated 4.0 Å, and 2.64 and 2.75 Å vs. 3.4 Å. The angles ∠C(5)C(1)C(2), ∠C(6)C(2)C(1), ∠C(5)C(1)C(4), ∠C(6)C(2)C(3), ∠C(8)C(4)C(1), and ∠C(7)C(3)C(2) have values in the range 115.5-117.5°, rather than the tetrahedral value, reflecting the angle strain presumably associated with the steric crowding.

The bond angles within the phosphate ring of **11** are comparable to those observed in the cyclic acyl phosphotriester[20] **12**; in both compounds, ∠OPO ~ 98, ∠POC > 113, and ∠OCC < 106°. In the cyclic enediol phosphotriester[21] **13**, ∠OPO ~ 98, ∠POC ~ 109 or slightly lower, and ∠OCC ~ 109° or larger. The small value of ∠OPO has also been encountered in other five-membered cyclic saturated phosphotriesters.[22,23]

The PO_4 group in **11** is a highly distorted tetrahedron, and these distortions are also observed in the two other phosphotriesters **12** and **13**[24]. The ring is virtually planar in **13** and nearly planar in **12**.



12



13

The endocyclic P-O(3) and P-O(4) bonds[25,26] are somewhat longer than the exocyclic P-O(1) and P-O(2) bonds in **11**. The C-O bond lengths fall into three categories: phosphate C(1)-O(3) ~ C(2)-O(4) > endocyclic ketal C(3)-O(5) ~ C(4)-O(5) > exocyclic ketal C(3)-O(6) ~ C(4)-O(7). The ether bonds C(9)-O(6) ~ C(10)-O(7) are similar in length to the endocyclic ketal bonds.

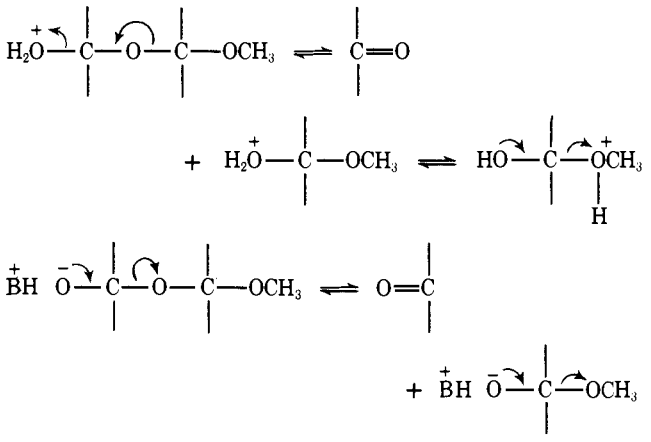
The intermolecular O(1)···O(2) distance is 2.486 (3) Å, which indicates the presence of hydrogen bonding between the adjacent phosphate groups.

Molecular Rearrangement of the Hemiketal Triester (8 or 10) into the Ketal Diester (11). The following facts must be considered in a discussion of possible mechanisms for this rearrangement: (a) The isomerization takes place cleanly in acetonitrile and not in chloroform, which suggests an important role for the polarity of the aprotic solvent. (b) The isomerization is prevented by the addition of diisopropylethylamine to the acetonitrile solution, as would be expected if the reaction is acid catalyzed. The rearrangement product, **11**, is acidic, and, moreover, the starting material, **8** or **10**, is extremely sensitive toward water, which ensures the presence of traces of acid in the samples of the hemiketal triester;[9] this point will be discussed below. (c) The methoxy group appears on the anomeric carbon of the ketal diester in the exo configuration, i.e., cis to the bridgehead methyls. This is the sterically favored isomer, and there is no evidence, from the ^1H NMR studies, that a second isomer of **11** precedes its appearance in the solution.

Table VI. Some Intramolecular Nonbonded Distances <3.0 Å

C(5)···O(7)	2.643 (3)	O(5)···H(7C)	2.53 (6)
C(6)···O(6)	2.754 (3)	O(5)···H(8C)	2.56 (6)
O(6)···O(7)	2.926 (3)	O(5)···H(9B)	2.55 (6)
C(5)···C(6)	2.946 (5)	O(5)···H(10B)	2.55 (6)
O(2)···H(7C)	2.42 (6)	O(6)···H(6B)	2.49 (6)
O(3)···H(5B)	2.56 (6)	O(7)···H(5C)	2.42 (6)
O(4)···H(6A)	2.63 (6)	O(7)···H(8B)	2.62 (6)
O(4)···H(7C)	2.38 (6)	H(5A)···H(6A)	2.39 (7)
		H(7A)···H(9A)	2.32 (7)
		H(8C)···H(10B)	2.24 (7)
		H(9C)···H(10A)	2.36 (7)

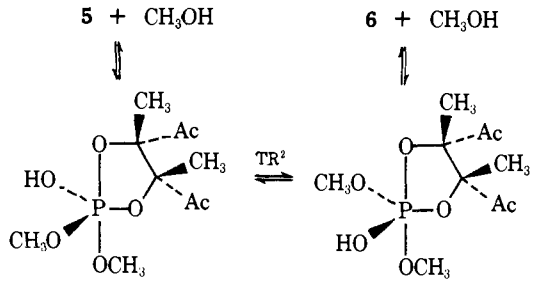
It should be recognized that several acid- and base-catalyzed equilibria exist in the solutions of the hemiketal triester: **8** ⇌ **7** ⇌ **5** + CH_3OH; **10** ⇌ **9** ⇌ **6** + CH_3OH. These equilibria allow an interconversion of the four diastereomers of **8** among themselves, and of the four diastereomers of **10** among themselves.



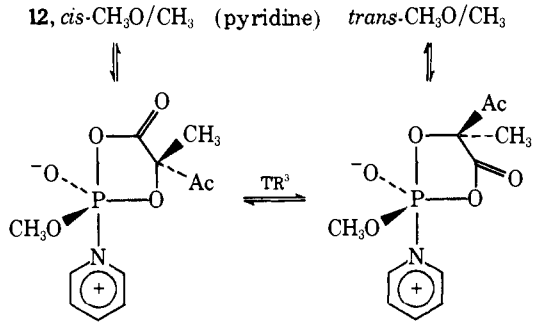
The facile stereomutation *at phosphorus* among cyclic phosphotriesters under catalysis by traces of methanol is a known phenomenon,[9,11] **5** ⇌ **6**; this has been interpreted as involving the transformation of P(4)[27-30] into P(5), followed by a permutational isomerization, probably according to the double turnstile rotation (TR^2) mechanism,[14,31] with the ring as ligand pair (Scheme I). Analogous stereomutations at phosphorus are promoted by tertiary amines, as has been shown in the case of the cyclic acyl phosphate,[32] **12** (Scheme II). The stereomutation at phosphorus results in interconversion of members of the *exo*- and *endo*-OCH_3 families, at the acyclic and the cyclic hemiketal stages, **7** ⇌ **9** and **8** ⇌ **10**, as well as at the stage of their precursors, **5** ⇌ **6**.

The acid-catalyzed equilibrations and the methanol-catalyzed stereomutation at phosphorus require that all possible stereoisomers of the cyclic and the acyclic hemiketals, **8**, **10**, **7**, and **9**, should be regarded as possible substrates for the rearrangement. However, the following speculations based on the configurations **8-I** (α or β) accommodate the known facts (Scheme **III**) (an analogous mechanism can be written from

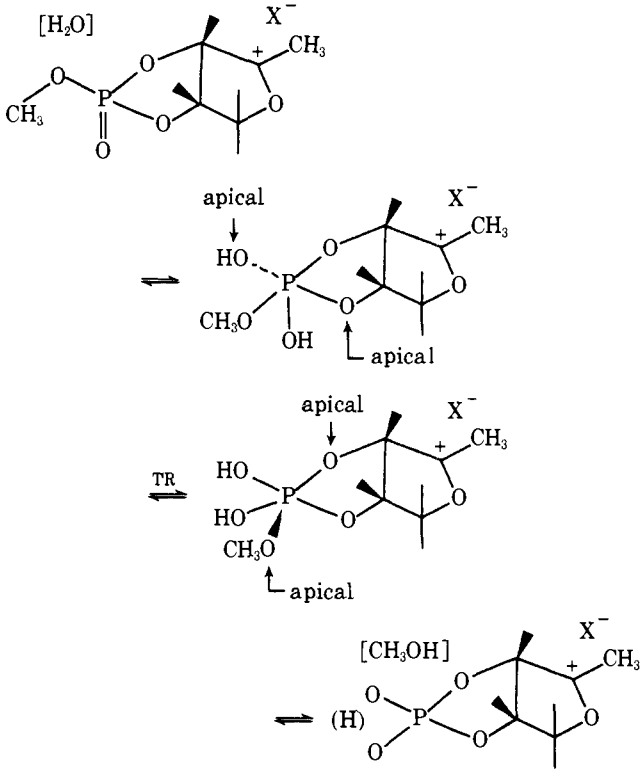
Scheme I



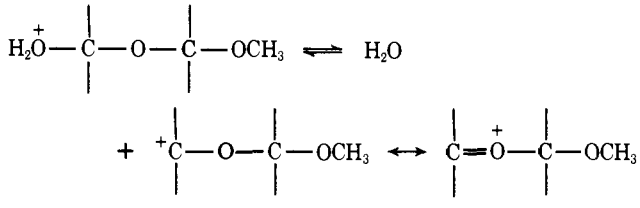
Scheme II



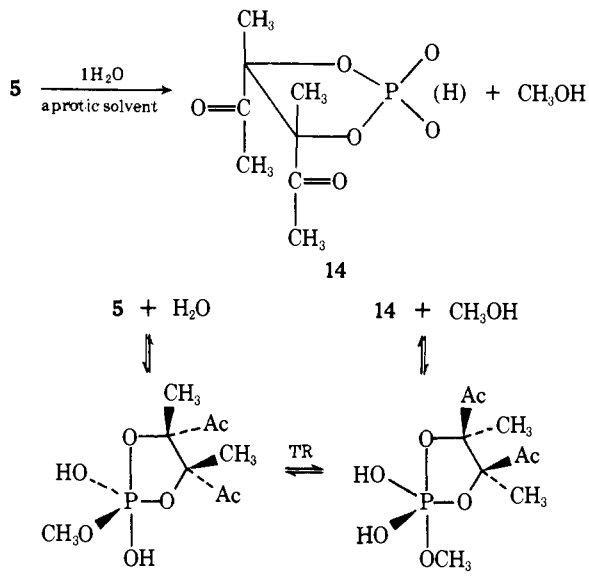
Scheme III



10-I). The observed acid catalysis of the rearrangement supports this mechanism, since the formation of the resonance-stabilized tertiary carbonium ion should be catalyzed by acids (but not by bases). One of the steps in Scheme III involves the addition of H_2O to P(4), and is entirely analogous to the mechanism suggested[15,29] to explain the extremely rapid conversion of the five-membered cyclic phosphotriester **5**, into

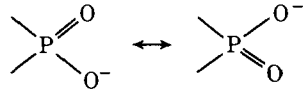


Scheme IV



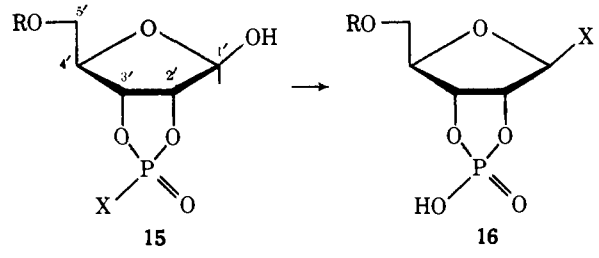
the cyclic phosphodiester **14** by 1 mol equiv of water in aprotic solvents (Scheme IV).

The following factors may contribute to the driving force of the rearrangement: (i) the relief of strain as a result of the formation of the carbonium ion; (ii) the relative stability of the latter, which is tertiary and capable of resonance stabilization by the oxygen substituent; (iii) the tendency of five-membered cyclic phosphates to form an oxyphosphorane,[33] as reflected in the rapid reactions illustrated in Schemes I-III; (iv) the development of acidity as a result of the rearrangement, which enhances proton dissociation and resonance stabilization of phosphorus



relative to the hemiketal triester starting material. This factor presumably offsets the adverse steric effect which results when the methoxy group reenters the anomeric carbon in the final product, **11**, since the methoxy group is bulkier than the OH group, and the space around the anomeric carbon is more restricted than that around the phosphorus, as shown by the x-ray analysis.

The anomeric carbons of the furanose structure of aldoses and ketoses differ in their degree of substitution (secondary and tertiary, respectively). This affects the stability of the respective carbonium ions (less favored in aldoses than in ketoses). Consequently, a group translocation involving the anomeric carbon and the phosphate phosphorus is less likely to occur in derivatives of aldoses than in those of ketoses. Nevertheless, the rearrangement is potentially significant in both sugar types, and it should be considered in discussions of the chemistry of D-ribofuranose 2′- and 3′-phosphates which are capable of forming a five-membered 2′,3′-cyclophosphate **15** quite easily. The requirements for the rearrangement **15** → **16** are acid catalysis and a moderately nucleophilic group, X,



15 **16**

on phosphorus. The isomerization is promoted by the development of the strong acidity, >P(O)OH, and is made possible by the tendency of five-membered cyclic phosphates to form the corresponding cyclic oxyphosphoranes.

Supplementary Material Available: Table III, A. Carbon-Hydrogen Bond Distances (Å) and Angles (deg), B. Calculated Hydrogen Atom Positions, and Table IV, Structure Factors (19 pages). Ordering information is given on any current masthead page.

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Reaction of the Neurotoxin Gabaculine with Pyridoxal Phosphate

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Abstract: The naturally occurring neurotoxin gabaculine (5-amino-1,3-cyclohexadienyl carboxylate) is a potent irreversible inhibitor of pyridoxal phosphate linked γ-aminobutyrate (GABA):α-ketoglutarate transaminase. The mechanism of inhibition requires the catalytic turnover of gabaculine to give an activated intermediate which reacts with the holoenzyme. In this report we show that gabaculine itself reacts with pyridoxal phosphate to afford *N-m*-carboxyphenylpyridoxamine phosphate (CPP_P). The limiting pseudo-first-order rate constant for its formation at 70 °C is 3.2×10^{-3} min^{-1} and the activation energy for its formation is 24.8 kcal/mol. The mechanism of CPP_P formation involves Schiff base formation between gabaculine and pyridoxal phosphate followed by a rate-limiting transamination reaction. A deuterium isotope effect of 4.26 is exhibited at this step. The activated transaminated intermediate spontaneously aromatizes to afford the highly fluorescent CPP_P. This is the first demonstration of a discrete chemical reaction between a naturally occurring irreversible enzyme inhibitor and pyridoxal phosphate.

Gabaculine is a naturally occurring small molecule neurotoxin isolated from *Streptomyces toyocaenis*.[1] When administered to animals it causes a dramatic increase in brain levels of the inhibitory neurotransmitter γ-aminobutyric acid (GABA). We have found that gabaculine irreversibly inhibits pyridoxal phosphate linked γ-aminobutyric acid (GABA): α-ketoglutaric acid transaminase.[2] This molecule is in a class of highly specific irreversible enzyme inhibitors that require