Organic and Biological Chemistry

The Crystal and Molecular Structure of Acetoinenediol Cyclophosphate

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Abstract: The enediol cyclic phosphate derived from acetoin was prepared by the controlled hydrolysis of 2,2,2-trimethoxy-4,5-dimethyl-1,3,2-dioxaphospholene. Acetoinenediol cyclophosphate was extremely reactive toward nucleophiles. The reaction with 1 mole equiv of methanol at 20° gave the enol form of dimethylphosphoacetoin, which then tautomerized to the keto form. Acetoinenediol cyclophosphate crystallized in space group $P2_1/n$ with lattice parameters $a = 7.755$, $b = 9.446$, $c = 10.345$ A, $\beta = 99.65°$. A three-dimensional X-ray structural analysis using 479 visually estimated intensities was refined to an R of 10.7%, refining positional and anisotropic thermal parameters. The ring system is planar and the methoxy group lies directly above the ring, with the carbon atom approximately centered between the two ring oxygens. The P–O distances in the ring were 1.59 and 1.57, the P–O distance to the methoxy group was 1.53, and the phosphoryl P–O distance was 1.38 A. The distances around the C=C suggested some delocalization of electrons within the ring. It was concluded that the phosphotriester with an unsaturated five-membered ring possessed a large amount of ring strain. The addition of methanol and of water to the phosphoryl group to give a relatively stable *intermediate* with pentacoordinated phosphorus should be a favorable process. This should account for the high reactivity of acetoinenediol cyclophosphate in solvolytic reactions. The hydrolysis of the five-membered cyclic pentaoxyphosphorane and the hydrolysis and methanolysis of the enediol cyclic phosphate were regarded as proceeding *via* analogous *intermediates* with pentacoordinated phosphorus.

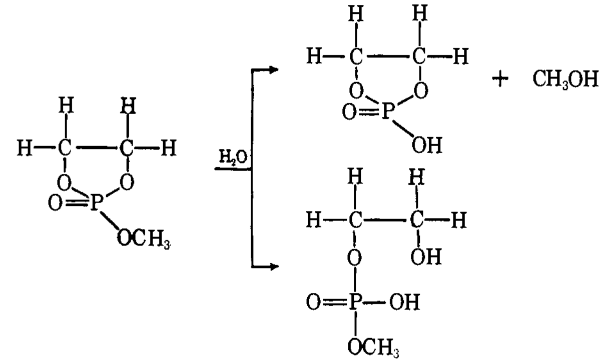
The recognition of the role played by five-membered cyclic phosphates in determining the behavior of glycerol phosphodiesters and of the ribonucleic acids has led to much research in this field.[2a,b]

Westheimer and his co-workers[2c–j] carried out an extensive study of the rate of hydrolysis of ethylene hydrogen phosphate and of methyl ethylene phosphate under a variety of conditions. They measured also the heat of hydrolysis of the cyclic phosphotriester. The main conclusion of these investigations was that the increase in the rate of hydrolysis of a five-membered cyclic phosphate relative to that of the corresponding open-chain analog was largely caused by strain in the cyclic ester. The hydrolyses were discussed[2f] in terms of an activated complex (transition state) or of an intermediate with pentavalent phosphorus.

This picture of the hydrolyses of the five-membered cyclic phosphates was complicated somewhat by the observation[2f] that the acid-catalyzed hydrolysis of ethylene hydrogen phosphate in water enriched with O^{18} was accompanied by exchange of heavy oxygen into unreacted ester. Interestingly enough, the exchange reaction, as well as the hydrolysis reaction, was strongly accelerated as a result of the presence of a five-membered ring. It was pointed out by Haake and Westheimer[2f] that "since strain is not relieved in the products of the exchange reaction (as it is in that of hydrolysis), these findings bear on the mechanism of the exchange reaction of phosphate esters."

Another point of interest related to the strain associated with the five-membered cyclic phosphates pertains to the direction of the hydrolytic cleavage of the phosphotriesters (Scheme I).

Scheme I



The alkaline hydrolysis of methyl ethylene phosphate occurred with P–O fission and complete ring opening.[2f,g] The hydrolysis of the phosphotriester in acid solution

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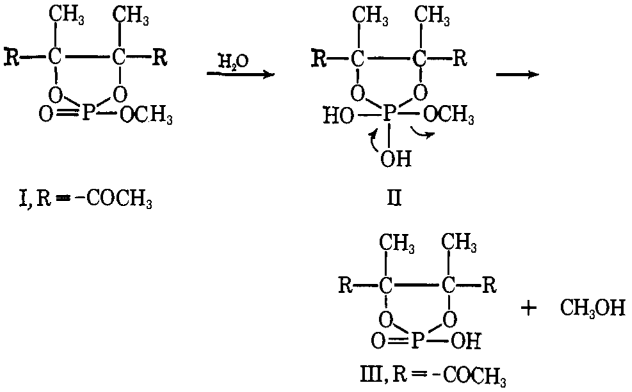
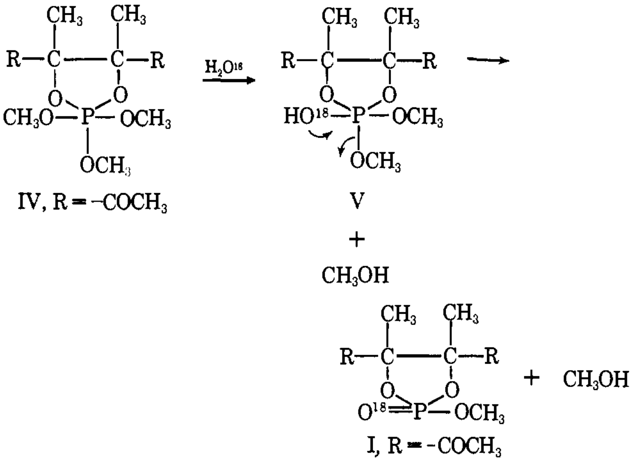
[2] For recent summaries with pertinent bibliographies, see (a) H. G. Khorana, "Some Recent Developments in the Chemistry of Phosphate Esters of Biological Interest," John Wiley and Sons, Inc., New York, N. Y., 1961, Chapter 3; (b) A. Todd, *Proc. Chem. Soc.*, 199 (1962); (c) J. Kumamoto and F. H. Westheimer, *J. Am. Chem. Soc.*, 77, 2515 (1955); (d) J. Kumamoto, J. R. Cox, Jr., and F. H. Westheimer, *ibid.*, **78**, 4858 (1956); (e) J. R. Cox, Jr., R. E. Wall, and F. H. Westheimer, *Chem. Ind.* (London), 929 (1959); (f) P. C. Haake and F. H. Westheimer, *J. Am. Chem. Soc.*, **83**, 1102 (1961); (g) M. Panar, E. T. Kaiser, and F. H. Westheimer, *ibid.*, **85**, 602 (1963); (h) F. Covitz and F. H. Westheimer, *ibid.*, **85**, 1774 (1963); (i) A. Eberhard and F. H. Westheimer, *ibid.*, **87**, 253 (1965); (j) D. A. Usher, E. A. Dennis, and F. H. Westheimer, *ibid.*, **87**, 2320 (1965).

involved mainly ring opening but afforded also some ethylene hydrogen phosphate. The amount of cyclic phosphodiester obtained varied from 5 to 30% depending on certain medium effects. Ramirez and his coworkers[3] observed *complete ring retention* when 1 mole equiv of water was added to the five-membered cyclic phosphotriester I in benzene solution at 20°. Other five-membered cyclic phosphotriesters related to furanose 2,3-cyclophosphates exhibited the same behavior. These authors[3] suggested that these extremely rapid hydrolyses with ring retention involved a cyclic dihydroxytrialkoxyphosphorane intermediate, II.

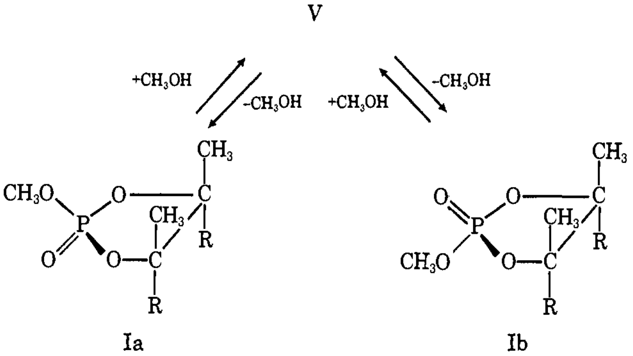


I, R = -COCH$_3$ II   III, R = -COCH$_3$

The hypothetical intermediate, II, should collapse to the cyclic diester, III, since the hydrolysis of the stable pentaalkoxyphosphorane, IV, gave the five-membered cyclic triester, I. Experiments with H_2O^{18} showed that the oxygen of the H_2O^{18} became the oxygen of the phosphoryl of the cyclic triester, I. This is understandable if the intermediate hydroxytetraalkoxyphosphorane, V, collapsed to I with ring retention, just as intermediate II collapsed to III with ring retention. Ramirez, *et al.*,[4] observed the formation of two diastereomers at phosphorus, Ia and Ib, of the five-membered cyclic triester in the hydrolysis of the oxyphosphorane, IV. They noted a rapid stereomutation at phosphorus caused by traces of methanol. They pictured the isomerization as involving the addition of methanol to the phosphoryl group of the triesters Ia and Ib to give the same intermediate, V, which was postulated in the hydrolysis of the pentaoxyphosphorane, IV.



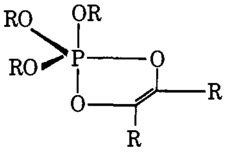
IV, R = -COCH$_3$ V   I, R = -COCH$_3$



Ia   Ib

Recently, Dennis and Westheimer[5] concluded that the hydrolysis of five-membered cyclic phosphates and phosphonates proceeded *via* intermediates with pentacoordinated phosphorus. They based this conclusion on certain considerations dealing with the phenomenon of pseudo-rotation in the trigonal-bipyramidal structure of the pentaoxyphosphoranes.[5] Aksnes and Bergesen[6] have postulated intermediates with pentavalent phosphorus in similar hydrolyses. Collin[7] discussed the electronic structure of five-membered cyclic phosphates.

The structure of a stable five-membered cyclic pentaalkoxyphosphorane was recently established by X-ray analysis.[8] As shown in formula VI, the unsaturated five-membered ring occupied an apical–equatorial plane in a trigonal bipyramid. This is the type of geometry which had been postulated by Haake and Westheimer[2f] for the *transition state* in the acid-catalyzed hydrolysis of ethylene hydrogen phosphate where the ring is saturated.



VI

There is little doubt that the *saturated* five-membered cyclic phosphate esters are more strained than the corresponding open-chain phosphate esters.[2c-j] On the other hand, pentaalkoxyphosphoranes having a saturated five-membered ring[9] are considerably more stable than those lacking the ring.[10] In fact, pentaalkoxyphosphoranes with an *unsaturated* five-membered ring like VI are also quite stable. It should be of considerable interest to correlate the molecular structure and the reactivity of the unsaturated cyclic pentaoxyphosphoranes with those of the corresponding unsaturated cyclic phosphate esters. This paper reports the first preparation and the crystal and molecular structure of one of these cyclic phosphates.[11]

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

(4) (a) F. Ramirez, N. B. Desai, and N. Ramanathan, *ibid.*, **85**, 1874 (1963); (b) *ibid.*, **85**, 3465 (1963).

(5) E. A. Dennis and F. H. Westheimer, *ibid.*, **88**, 3431, 3432 (1966).

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

(7) R. L. Collin, *J. Am. Chem. Soc.*, **88**, 3281 (1966).

(8) (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).

(9) For recent reviews of this question, see (a) F. Ramirez, *Bull. Soc. Chim. France*, 2443 (1966); (b) *Pure Appl. Chem.*, **9**, 337 (1964); (c) F. Ramirez, A. V. Patwardhan, H. J. Kugler, and C. P. Smith, *Tetrahedron Letters*, 3053 (1966).

(10) D. B. Denney and S. T. D. Gough, *J. Am. Chem. Soc.*, 87, 138 (1965).

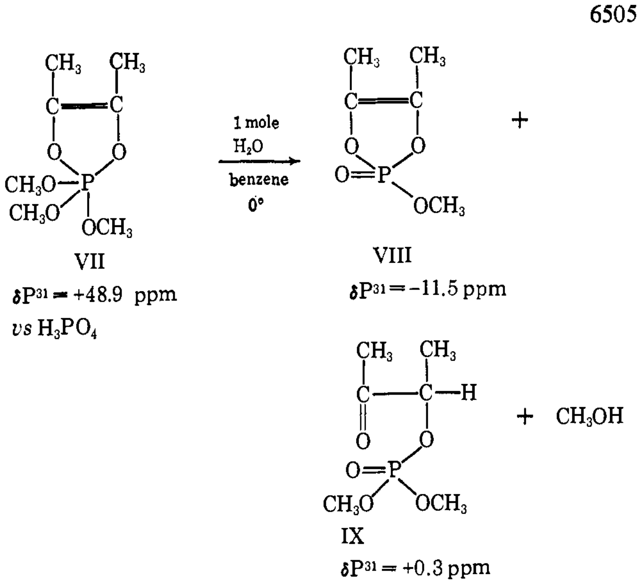
(11) A preliminary communication has appeared: F. Ramirez, O. P. Madan, and C. P. Smith, *J. Am. Chem. Soc.*, **87**, 670 (1965).

The structures of two saturated five-membered cyclic phosphate esters have been reported.[12,13] Newton, Cox, and Bertrand have suggested that in the five-membered cyclic phosphates, one of the phosphorus d orbitals is not used in π bonding and the availability of such an orbital facilitates both the nucleophilic attack at phosphorus as well as the formation of a transition state with sp^{3}d hybridization. If such a decrease in π bonding does occur, it does not seem to be reflected in the bond lengths, since there is no significant difference in P–O bond lengths in the five-membered cyclic phosphotriesters so far studied and acyclic triesters.[14] Differences in P–O bond length attributed to differences in pd π bonding were observed in the cyclic pentaoxyphosphoranes, VI.[8] Thus, the apical P–O bond forming part of the ring was longer than the apical P–O bonds of the alkoxy groups; likewise, the equatorial P–O bond of the ring was longer than the equatorial P–O bonds of the alkoxy groups. This was attributed to a decrease in pd π bonding involving the oxygen atoms of the phospholene ring and the phosphorus. Therefore, the bonds to the ring do not show the shortening caused by π bonding relative to the expected single bond distances which is apparent for the alkoxy groups. The apical bond to the ring had just the length, 1.76 A, suggested by Cruickshank for a P–O single bond.[15]

Results

Preparation of Acetoinenediol Cyclophosphate (VIII). 2,2,2-Trimethoxy-4,5-dimethyl-2,2-dihydro-1,3,2-dioxaphospholene (VII) was prepared from the reaction of biacetyl, $CH_3COCOCH_3$, with trimethyl phosphite, $(CH_3O)_3P$.[16–18] The phospholene was converted into the five-membered cyclic phosphotriester VIII by 1 mole equiv of water in benzene solution under the conditions specified in the Experimental Section. When the temperature was kept low, only traces of trimethyl phosphate were produced. In all cases, however, the cyclic phosphotriester VIII was accompanied by the open-chain phosphotriester, dimethylphosphoacetoin (IX). The optimum conditions gave the cyclic and the open phosphates in a 1:2.4 proportion, respectively.

Part of the dimethylphosphoacetoin (IX) was produced from the cyclic phosphotriester VIII by reaction with the methanol produced during the hydrolysis of the pentaoxyphosphorane VII. This could be shown by an independent experiment involving the cyclic phosphate VIII and 1 mole equiv of methanol. *There is no precedent in the literature for such rapid methanolysis of a phospho triester of any type, i.e., open chain or cyclic.*



VII

$\delta P^{31} = +48.9$ ppm *vs* H_3PO_4

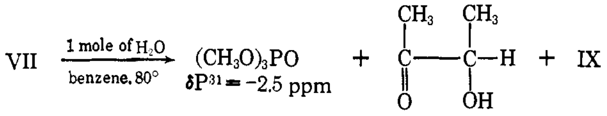
VIII

$\delta P^{31} = -11.5$ ppm

IX

$\delta P^{31} = +0.3$ ppm

When the hydrolysis of the pentaoxyphosphorane VII by 1 mole equiv of water in benzene solution was allowed to proceed without careful control of the temperature, different results were observed. Under these conditions, very little cyclic phosphotriester was obtained; the major products were trimethyl phosphate and dimethylphosphoacetoin (IX). The trimethyl phosphate was not produced by methanolysis of the phosphoacetoin IX; therefore, it must stem from some unstable intermediate. The possible mechanism of these reactions will be discussed below.



$$\text{VII} \xrightarrow[\text{benzene, } 80^\circ]{\text{1 mole of } H_2O} \underset{\delta P^{31} = -2.5 \text{ ppm}}{(CH_3O)_3PO} + CH_3C(=O)CH(OH)CH_3 + \text{IX}$$

The structure of the cyclic phosphate VIII was based on the negative value of the P^{31} nmr shift which is characteristic of five-membered cyclic phosphates.[19] Moreover, the H^1 nmr spectra showed a 3 H doublet, $J_{HP} = 11.5$ cps at τ 6.24, due to one methoxy group. The two methyl groups attached to the olefinic double bond gave a singlet at τ 8.10.

X-Ray Crystallographic Analysis. The results obtained by the methods described in the Experimental Section are shown in Figures 1 and 2. Figure 1 shows the projection of the structure on the *bc* plane and Figure 2 shows a diagram of the molecule with some bond distances. The bond distances are listed in Table I and the bond angles in Table II.

The dioxaphospholene ring is planar. The plane of the ring includes the two exocyclic methyl groups, C(3) and C(4). This plane forms a dihedral angle close to 90° with another plane which includes the atoms C(5), O(2), P(1), and O(4). The carbon of the methoxy group, C(5), points directly back over the ring and is centered between the two oxygen atoms of the ring, O(1) and

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(12) T. A. Steitz and W. N. Lipscomb, *J. Am. Chem. Soc.*, **87**, 2488 (1965).

(13) M. G. Newton, J. R. Cox, Jr., and J. A. Bertrand, *ibid.*, **88**, 1503 (1966).

(14) G. Svetich and C. N. Caughlan, *Acta Cryst.*, **19**, 645 (1965).

(15) D. W. J. Cruickshank, *J. Chem. Soc.*, 5486 (1961).

(16) (a) F. Ramirez and N. B. Desai, *J. Am. Chem. Soc.*, **82**, 2652 (1960); (b) F. Ramirez and N. B. Desai, *ibid.*, **85**, 3252 (1963); (c) the method of preparation described in ref 16a and 16b was based on the mode of reaction of trialkyl phosphites with quinones, first reported by F. Ramirez and S. Dershowitz, *J. Org. Chem.*, **22**, 856 (1957), and **23**, 778 (1958).

(17) The biacetyl-trialkyl phosphite adduct was also reported by 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 101P, and G. H. Birum and J. L. Dever, U. S. Patents 2,961,455 (1960) and 3,014,949 (1961).

(18) The biacetyl–trialkyl phosphite reaction was described also by V. A. Kukhtin, *Dokl. Akad. Nauk SSSR*, **121**, 466 (1958); *Chem. Abstr*, **53**, 1105*b* (1959). These authors gave conflicting structures for the products. V. A. Kukhtin and K. M. Orekhova, *J. Gen. Chem. USSR*, **30**, 1229 (1960); *Chem. Abstr.*, **55**, 358*i* (1961); V. A. Kukhtin, K. M. Kirillova, and R. R. Shagidullin, *Zh. Obshch. Khim.*, **32**, 649 (1962); *Chem. Abstr.*, **58**, 546*h* (1963); V. A. Kukhtin and K. M. Kirillova, *J. Gen. Chem. USSR*, **32**, 2755 (1962).

(19) (a) R. A. Y. Jones and A. R. Katritzky, *J. Chem. Soc.*, 4376 (1960); (b) F. Ramirez, A. V. Patwardhan, N. B. Desai, and S. R. Heller, *J. Am. Chem. Soc.*, **87**, 549 (1965); (c) F. Ramirez, *et al.*, Abstracts of Papers, IUPAC Symposium on Organophosphorus Compounds, Heidelberg, Germany, May 20, 1964; (d) G. M. Blackburn, J. S. Cohen, and A. Todd, *Tetrahedron Letters*, 2873 (1964).

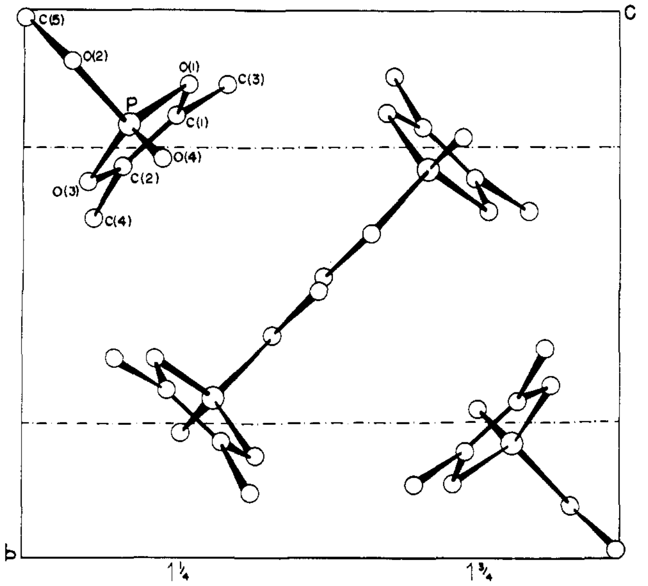

Figure 1. Projection of the crystal structure of acetoinenediol cyclophosphate onto the *bc* plane.

Table I. Bond Distances in Acetoinenediol Cyclophosphate

P-O(1)	1.59 (2)[a]
P-O(2)	1.53 (2)
P-O(3)	1.57 (2)
P-O(4)	1.38 (3)
P-C(1)	2.42 (3)
P-C(2)	2.37 (2)
P-C(3)	3.77 (3)
P-C(4)	3.75 (3)
P-C(5)	2.61 (4)
O(1)-C(1)	1.36 (4)
O(1)-C(2)	2.20 (4)
O(1)-O(3)	2.39 (2)
O(2)-C(5)	1.44 (5)
O(2)-O(1)	2.51 (2)
O(2)-O(3)	2.52 (2)
O(2)-O(4)	2.38 (4)
O(3)-C(2)	1.39 (3)
O(3)-C(1)	2.30 (4)
C(1)-C(2)	1.33 (4)
C(1)-C(3)	1.46 (4)
C(2)-C(4)	1.47 (4)
C(5)-O(1)	3.04 (3)
C(5)-O(3)	3.07 (4)

[a] The number in parentheses is the standard deviation and refers to the least significant digits.

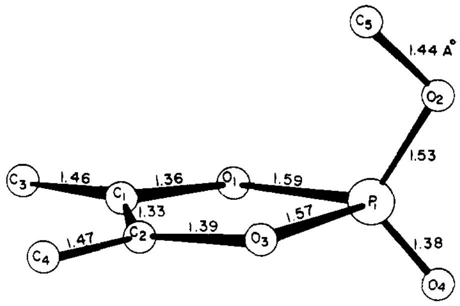

Figure 2. Molecular structure of acetoinenediol cyclophosphate.

O(3), to within the accuracy of the determination; this C(5) carbon is 2.61 A above the plane of the ring. The orientation of the methoxy group is identical with that found in methyl ethylene phosphate,[12] but it differs by 180° from that found in methyl pinacol phosphate.[13] The C(5)-O(1) and the C(5)-O(3) distances are 3.04 and 3.07 A, very similar to those found in methyl ethylene phosphate[12,13] (3.01 and 2.98 A). These distances are within the range of possible hydrogen bonding; however, it seems unlikely that hydrogen bonding of this type between a methoxy group and the oxygen of a phosphate could account for the orientation of the methoxy group. The hydrogen positions could not be determined.

The P-O distances in the ring are slightly longer than the P-OCH_3 distance. This difference is of the order of 2-3 standard deviations and may be significant. The P-O distance of the phosphoryl group (1.38 A) is somewhat shorter than the corresponding distance in other phosphotriesters (1.44 A); again, this may be a significant difference. It should be noted that the phosphoryl group gives rise to strong bands in the infrared spectrum of this substance in carbon tetrachloride solution at 1316 and 1300 cm^{-1} (7.60 and 7.69 μ); these bands are at a slightly higher frequency than those found in open-chain phosphotriesters.[20]

Table II. Bond Angles in Acetoinenediol Cyclophosphate

O(1)-P-O(2)	106.8 (6)
O(2)-P-O(3)	108.9 (7)
P-O(1)-C(1)	109.8 (11)
O(3)-C(2)-C(1)	115.3 (16)
C(3)-C(1)-C(2)	135.1 (18)
O(1)-P-O(3)	98.5 (6)
O(2)-P-O(4)	109.5 (8)
P-O(3)-C(2)	106.0 (11)
O(1)-C(1)-C(3)	114.7 (16)
C(4)-C(2)-C(1)	130.1 (17)
O(1)-P-O(4)	116.8 (6)
O(3)-P-O(4)	115.6 (7)
O(1)-C(1)-C(2)	110.2 (17)
O(3)-C(2)-C(4)	114.3 (14)
P-O(2)-C(5)	122.9 (9)
O(2)-P-C(1)	116.2 (7)
O(2)-P-C(2)	116.7 (7)
O(2)-P-C(3)	114.7 (6)
O(2)-P-C(4)	116.4 (6)

The C-O distances are of interest. The methoxyl distance, C(5)-O(2), is normal (1.44 A), but the two C-O distances in the ring are significantly shortened (1.36, 1.39 A). The C-C distances between the methyl groups and the ring, C(1)-C(3) and C(2)-C(4), are somewhat shorter than those of normal C-C single bonds (1.54 A). Concerning bond angles, several significant features are noted. (1) The two P-O-C angles in the ring, P-O(1)-C(1) and P-O(3)-C(2), are somewhat smaller than those in methyl ethylene phosphate[12] and methyl pinacol phosphate.[13] (2) Apparently the repulsion between the two methyl groups on the ring, C(3) and C(4), led to an increase in the angles, C(3)-C(1)-C(2) and C(4)-C(2)-C(1), to 135 and 130°. The corresponding angles to oxygen, C(3)-C(1)-O(1) and C(4)-

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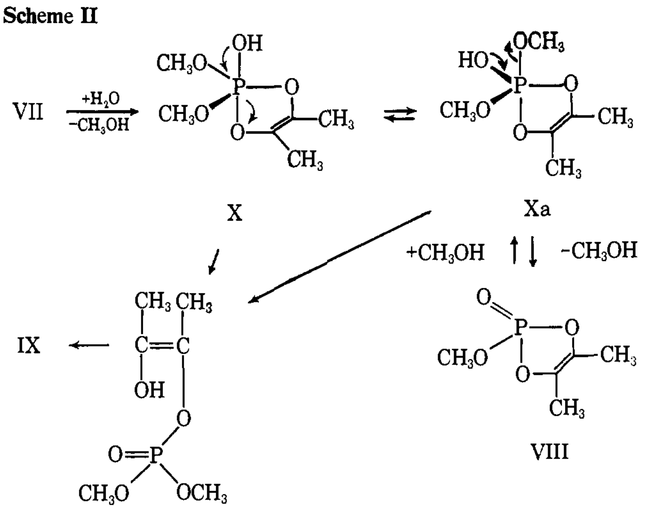
(20) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954, p 312.

C(2)–C(3), have decreased to 114°. (3) The ring angle at phosphorus, O(1)–P–O(3), is essentially the same as that found in the other five-membered cyclic phosphates.[12,13]

Discussion

Hydrolysis of the Pentaoxyphosphorane with an Unsaturated Five-Membered Ring (VII). The behavior of the five-membered cyclic unsaturated pentaoxyphosphorane toward water, in particular the remarkable variations of the course of the reaction with temperature and with the nature of the solvent, can be rationalized in the following manner.[11] Utilizing the geometry, VI, established in the crystalline state for one unsaturated pentaoxyphosphorane,[8] the nucleophilic substitution by the water on pentacovalent phosphorus can give rise to the hydroxytetraalkoxyphosphorane, X. In the process, the ring is preserved and the longer and weaker axial $P–OCH_3$ bond was assumed to have been broken.[20a] However, a very rapid positional exchange may take place to give structure Xa.[4–6,21–23] Structure Xa can collapse to acetoinenediol cyclophosphate (VIII) by rupture of an apical P–O bond or it may collapse to the enol form (IXa) of dimethylphosphoacetoin by rupture of another apical P–O bond. The enol form IXa can also be produced from X by rupture of an apical bond. In all cases, there was always more open phosphate (IXa) than cyclic phosphate (VIII), but the fact that the strained cyclic phosphate was formed at all is of considerable interest. This may be related to some stabilization of the ring or some other factor, but it is probably made possible by the extraordinary speed of these processes (Scheme II).[23a]

Scheme II

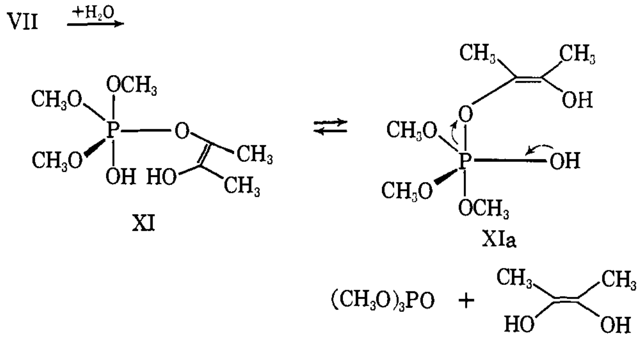


IXa, $\delta P^{31} = +2.5$ ppm

The extremely rapid methanolysis of acetoinenediol cyclophosphate (VIII) to dimethylphosphoacetoin (IX) is readily understandable since it involves simply the readdition of methanol to the phosphoryl group with formation of the common intermediate, Xa, which then collapses to IXa. Methanol probably does not add to the phosphoryl of open-chain phosphotriesters. The difference between five-membered cyclic and open phosphotriesters is probably due to two reinforcing factors: (1) the five-membered cyclic phosphate is considerably more strained than the open phosphate and (2) the pentaoxyphosphorane with a five-membered ring is much less strained than the pentaoxyphosphorane lacking the rings.[8,9a,10] Both of these factors make the phosphoryl addition mechanism an attractive one for the five-membered cyclic phosphates. The extraordinary speed of the methanolysis is demonstrated by the observation that addition of *1 mole equiv* of methanol to acetoinenediol cyclophosphate (VIII) at 20° caused the disappearance of VIII and the formation of the enol form IXa of dimethylphosphoacetoin; the latter then tautomerized to the keto form, IX. In other words the methanolysis of VIII is even more rapid than the ketonization of the enol, IXa.

The formation of trimethyl phosphate when the hydrolysis of oxyphosphorane VII was allowed to proceed near the boiling point of benzene suggests a second mechanism for the hydrolysis, since dimethylphosphoacetoin is not affected by water or by methanol under these conditions. Probably the nucleophilic substitution at the phosphorus of VII can also give rise to an open-chain intermediate, XI, under certain conditions. This intermediate, XIa, should collapse to trimethyl phosphate and acetoin rather than to dimethylphosphoacetoin (Scheme III).

Scheme III



Molecular Structure and Reactivity of Saturated and Unsaturated Five-Membered Cyclic Phosphate Esters. It seems reasonable that (1) if a five-membered cyclic phosphate ester is strained relative to an open phosphate ester or an unstrained cyclic phosphate and (2) if the pentaoxyphosphorane which is derived by addition of water or another nucleophile to the phosphoryl phosphorus is less strained when it has a five-membered ring than when it lacks it, due to intramolecular crowding in the trigonal bipyramid,[8] the hydrolysis of cyclic phosphotriesters[23b]

[20a] Note Added in Proof. The substitution at pentavalent phosphorus may be a concerted process, or it may involve a prior ionization with P–O bond fission. The concerted mechanism explains the retention of the ring as follows: a trigonal bipyramid 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. The concerted transition state resembles a trigonal bipyramid (*i.e.*, the reactant) because the reaction is highly exothermic. Hence, the ring should be preserved in that type of transition state.

[21] See ref 16b. These authors recognized that the three methoxy groups of the recently discovered phospholene, VII, gave only one doublet in the H^1 nmr spectrum. They stated that "the three methoxyl groups are equivalent or indistinguishable" (*cf.* p 3256). Further, "the methoxyls may exchange positions without rupture of a phosphorus–oxygen bond, or the phosphorane may be in equilibrium with very small amounts of a dipolar structure" (*cf.* p 3257).

[22] R. S. Berry, *J. Chem. Phys.*, **32**, 933 (1960).

[23] E. L. Muetterties and R. A. Schunn, *Quart. Rev.* (London), **20**, 245 (1966), and references therein.

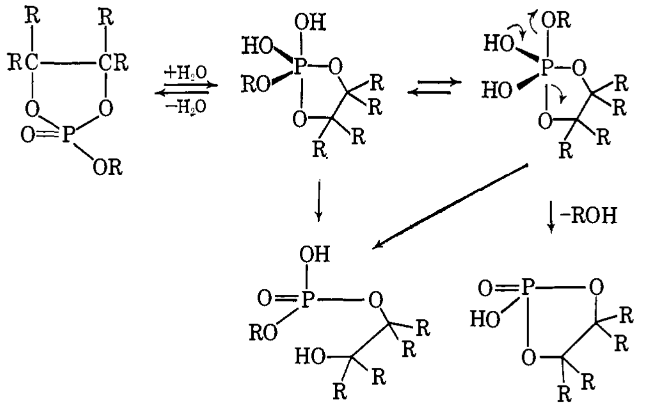
[23a] Note Added in Proof. The collapse of the oxyphosphorane is highly exothermic. The transition state resembles the reactant (trigonal bipyramid). The activation energy is lower if the ring is retained than if the ring is broken, for steric reasons.

[23b] Note Added in Proof. The alkaline hydrolysis of α-ketol phosphotriesters may involve carbonyl participation and oxyphosphorane formation of a related type. *Cf.* F. Ramirez, B. Hansen, and N. B. Desai, *J. Am. Chem. Soc.*, **84**, 4588 (1962).

and cyclic phosphodiesters could occur by the phosphoryl addition mechanism, at least under certain experimental conditions. This view has been recently expressed by several investigators[3,5–7] (Scheme IV).

In particular, Dennis and Westheimer[5] claimed to have provided solid evidence for the participation of intermediates with pentavalent phosphorus in the hydrolysis of the five-membered cyclic phosphates on the basis of arguments dealing with pseudo-rotation in compounds with pentacoordinated phosphorus.

Scheme IV



The relationship between the molecular structure of saturated cyclic phosphotriesters and the reactivity of these compounds has been discussed.[5,7,12,13] The present work provides the data for an *unsaturated* five-membered cyclic phosphate. *The data show that there is considerable ring strain in the molecule of acetoinenediol cyclophosphate.* Assuming the following normal bond angles (O–P–O, 109°; P–O–C, 120°; O–C–C, 120°; C–C–C, 120°) it can be seen that there is considerable strain in the P–O–C bonds and the bonds adjacent to the C═C double bond. A rough calculation of this strain indicates several kilocalories in excess of that in methyl ethylene phosphate.[24]

The strain resulting from the fact that the ring is planar appears to be one of the important factors in determining the reactivity of acetoinenediol cyclophosphate. The molecular structure of the unsaturated phosphate also suggests considerable delocalization of the electrons around the C═C bond. This delocalization appears as π bonding to O(1) and O(3), thus shortening these bonds. There seems to be a slight decrease in the π bonding of the phosphorus to O(1) and O(3), producing a lengthening of these bonds. There could also be an increase in π bonding to O(2) with a corresponding decrease in the bond length. The orientation of C(5) directly over the ring could be taken as indicative of the importance of the oxygen orientation for proper overlap of the p orbitals of the oxygen atom with the d orbitals of a phosphorus atom in the formation of π bonds.[13] If these considerations are valid, it can be seen that the withdrawal of electrons associated with O(1) and O(3) from the phosphorus would tend to increase the positive charge on the phosphorus. This would effect the shortening of a phosphoryl oxygen distance and should also account for part of the increase in the reactivity of acetoinenediol cyclophosphate toward nucleophiles.

Experimental Section

Preparation of 4,5-Dimethyl-2-methoxy-2-oxo-1,3,2-dioxaphospholene (Acetoinenediol Cyclophosphate). A stirred solution of the biacetyl–trimethyl phosphite 1:1 adduct[16] (VII) (19.97 g) in benzene (20 ml) was cooled in an ice–salt bath and treated with 1 mole equiv of water (1.71 g). The solution temperature went up from −4 to +18° within 2 min. The solvent was *immediately* removed under vacuum at 25°. The H^1 and P^{31} nmr spectra of the liquid residue showed the presence of the cyclic triester VIII and of dimethylphosphoacetoin (IX) in a 1:2.4 proportion; only traces of trimethyl phosphate were present. Distillation in a 24-in. spinning-band column gave acetoinenediol cyclophosphate (VIII), bp 48–49° (0.06 mm), $n^{25}\text{D}$ 1.4310, in 30% yield. On standing at 20°, the liquid VIII crystallized to colorless needles, mp 42–43°, not changed by recrystallization from benzene–hexane; the properties of the crystals and the liquid were identical.

Anal. Calcd for $C_5H_9O_4P$: C, 36.6; H, 5.5; P, 18.9. Found: C, 36.1; H, 5.6; P, 18.4.

Spectral values were H^1 nmr (τ in ppm), a 3 H doublet, $J_{HP} = 11.5$ cps, at 6.24 (CH_3O) and a 6 H singlet at 8.10 (CH_3 on olefin); P^{31} nmr (neat at 40.5 Mcps in ppm *vs.* 85% H_3PO_4); a 1:3:3:1 quartet, $J_{PH} = 12$ cps, at -11.5 ± 0.1. Strong bands in the infrared region (in CCl_4) were caused by the P═O stretching vibrations (7.60 and 7.69 μ), by the $POCH_3$ stretchings (9.48 and 8.40 μ), and by the vinyl C–O stretching (8.30 μ). Also strong bands were found at 8.85, 10.10, and 11.20 μ.

When 1 mole equiv of water was added very slowly in small portions over a 25-min period, while the temperature was kept below 5° by external cooling, no cyclic triester VIII was detected The product consisted mostly of the open triester IX and of small amounts of what could be the open diester, methylhydrogenphosphoacetoin.

When 1 mole equiv of water was added to a 10 *M* benzene solution of the phosphorane VII at 20°, the solution reached the boiling point of benzene. Under these conditions no cyclic ester VIII was obtained. The major products were trimethyl phosphate and dimethylphosphoacetoin, IX.

Under comparable conditions the hydrolysis of VII gave less cyclic ester VIII when carried out in ether than in benzene.

Conversion of Cyclic Triester, VIII, into Open Triester, IX. Equimolar amounts of the triester VIII and of methanol were mixed at 20°. The course of the reaction was followed by means of H^1 and P^{31} nmr spectra. Observations were made after 5 min and 1, 3, and 20 hr. More methanol was then added and the spectra were examined after 2 days. $\delta P^{31} = +0.2$ ppm for keto dimethylphosphoacetoin, +2.5 ppm for enol dimethylphosphoacetoin, and −2.5 ppm for trimethyl phosphate. The H^1 nmr of dimethylphosphoacetoin has been described.[19b] The enol form has a signal at τ 3.6.

After 5 min, the enol and the keto forms of the open triester IX were detectable. After 1 hr, two isomers of IX were still visible. After 20 hr, only keto IX was present. No changes were observed after 2 days in the presence of an excess of methanol.

X-Ray Analysis of Acetoinenediol Cyclophosphate (VIII). Crystals of acetoinenediol cyclophosphate were produced by the reaction of biacetyl–trimethyl phosphite 1:1 adduct with 1 mole equiv of water. Since the crystals hydrolyze in moist air, they were enclosed in Pyrex capillaries for the collection of X-ray data.[25] The crystal used for collection of X-ray data had dimensions of 0.3 × 0.5 × 0.55 mm. The lattice dimensions were determined on a GE XRD5 diffractometer and are $a = 7.755 \pm 0.005$, $b = 9.446 \pm 0.005$, $c = 10.345 \pm 0.005$ A, $\beta = 99.65 \pm 0.05°$. The conditions

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[24] The force constants used for this rough calculation were the midrange constants given by Usher, Dennis, and Westheimer,[2i] and a value of 50 kcal/radian² for the bending force constant around C═C calculated from an approximate value 0.32×10^{-11} erg/radian². F. H. Westheimer in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, Table I, pp 529. Using these values and calculating the strain energy by $E = \Sigma {}^1\!/_2 k(\Delta\nu)^2$, a value of E for methyl ethylene phosphate is about 5 kcal/mole while that for acetoinenediol cyclophosphate is about 10 kcal/mole. The major contribution toward this greater strain is the P–O–C angle and the angles around the C═C.

[25] Transfer of the crystal was accomplished in a drybox. It was also found that the crystals kept for some time under mineral oil and could be cut and placed in capillaries in oil. Lindeman capillaries were originally used but apparently there was enough moisture on the surface or diffusion through the thin walls to cause deterioration of the crystal within 1 week. Lattice parameters were collected on a GE XRD 5 diffractometer.

Table III. Atomic Coordinates

	x/a	y/b	z/c
P	0.3475 (8)	0.2092 (5)	0.1791 (4)
O(1)	0.2344 (22)	0.1359 (14)	0.2766 (10)
O(2)	0.3818 (16)	0.0958 (14)	0.0803 (12)
O(3)	0.2008 (17)	0.3141 (11)	0.1100 (11)
O(4)	0.5079 (21)	0.2705 (17)	0.2344 (14)
C(1)	0.0670 (32)	0.1923 (18)	0.2600 (15)
C(2)	0.0483 (25)	0.2888 (18)	0.1656 (16)
C(3)	−0.0470 (26)	0.1366 (20)	0.3483 (17)
C(4)	−0.1033 (26)	0.3834 (20)	0.1179 (17)
C(5)	0.2407 (31)	0.0140 (26)	0.0051 (21)

Table IV. Thermal Parameters and Mean-Square Displacement

							Mean-square displacement, A^2		
	$B(11)$[b]	$B(22)$	$B(33)$	$B(12)$	$B(13)$	$B(23)$	Max	Med	Min
P	1.51	1.48	2.30	−0.08	0.00	0.74	0.04	0.02	0.01
O(1)	3.20	3.53	2.28	−0.05	0.16	2.01	0.07	0.04	0.01
O(2)	2.20	4.04	4.16	0.82	1.29	−0.61	0.06	0.05	0.01
O(3)	1.20	1.62	3.24	1.35	0.82	1.44	0.06	0.02	0.01
O(4)	4.05	6.12	6.48	0.26	0.99	1.75	0.09	0.05	0.05
C(1)	3.85	2.58	1.64	−0.63	−1.62	−0.83	0.05	0.03	0.00
C(2)[a]	−2.47	5.04	4.31	−0.18	0.36	−2.65	0.05	0.03	0.02
C(3)[a]	2.43	3.36	4.22	−0.43	3.78	0.77	0.14	0.05	0.03
C(4)	2.93	4.33	3.13	2.49	−0.20	0.56	0.07	0.04	0.02
C(5)	2.50	5.16	4.85	0.63	1.25	−2.10	0.09	0.06	0.01

[a] The anisotropic temperature factors for C(2) and C(3) are nonpositive definite. For mean-square displacement, the β_{11} of C(2) and β_{13} and β_{23} of C(3) were set equal to 0.0001, which was less than the standard deviation. [b] Standard deviations of B_{ij}'s are approximately 0.2 for phosphorus and 0.5 for carbon and oxygen atoms.

Table V.[a] Equations of Least-Squares Planes Referred to Orthogonal Axes

	a	b	c	D, A	S, A^2
PO(2)O(4)C(5)	−0.0142	−0.6870	0.7265	−0.0759	63.0×10^{-6}
PO(1)O(3)C(1)C(2)C(3)C(4)	0.2206	0.7307	0.6460	3.2713	30.9×10^{-4}
PO(1)O(3)C(1)C(2)	0.1999	0.7312	0.6522	3.2411	39.1×10^{-5}

[a] $X = x + z \cos \beta$; $Y = y$; $Z = z \sin \beta$; $a\bar{X} + b\bar{Y} + c\bar{Z} = D$; S = sum of squares of deviation of atoms from plane; D = origin to plane distance in angstroms. All atoms are given equal weight.

for reflection, $k = 2n$ for the $0k0$ reflections and $h + l = 2n$ for the $h0l$ zone, indicate space group $P2_1/n$. The measured density is 1.417 g/cc and on the basis of four molecules per unit cell the calculated density is 1.464 g/cc. The linear absorption coefficient for Cu Kα radiation is 20.18 cm^{-1}.

The intensity data were collected on a Supper Weissenberg camera using nickel-filtered copper radiation and a combination of multiple film and timed exposure techniques. Levels zero through four were recorded while rotating about the ⟨100⟩ direction. The intensities of 479 independent reflections were estimated visually by comparing with a set of standard intensities and converted to structure factors in the usual manner.[26] No absorption corrections were made. For structure factor calculations, atomic form factors for phosphorus, oxygen, and carbon were from the literature.[27] Anomalous terms were not used.

Structure Determination and Refinement. The structure was deduced by interpretation of the Patterson function. The position of the phosphorus atom was readily found and the Fourier synthesis calculated from phases based on the phosphorus atom position indicated the positions of the oxygen atoms and two carbon atoms. Subsequent structure factor calculations and Fourier syntheses showed the entire structure.

Refinement started with the R factor at 39%. The initial refinement was carried out using a block diagonal program for the IBM 1620.[28] A number of cycles refining positional parameters and individual isotropic temperature factors reduced the R to 13.8%. In using the block diagonal least-squares refinement program a parameter shift damping factor of 0.25 was used initially but increased to 0.8 as the refinement progressed. Several cycles refining positional and anisotropic temperature factors[29] reduced the R factor to 11.7%.[30] The last two cycles of refinement used the full matrix refinement program of Busing, Martin, and Levy,[31] refining positional and anisotropic thermal parameters and five scale constants for level to level scaling. The final R factor is 10.7%.[32]

The final positional and thermal parameters with standard deviations are listed in Tables III and IV. Table IV also lists the mean-square amplitude of vibration along the principal axes of the thermal ellipsoid. For calculation of these an orthogonal coordinate system was used in which the x axis coincided with a and the y axis coincided with b. The bond lengths and bond angles with standard deviations are listed in Tables I and II. Table V shows the equations for the best least-squares planes for the phosphorus ring system with and without the methyl groups and for the phosphorus, phosphoryl oxygen, methoxy plane.[33] The structure factor table has been deposited as Document No. 9536 with the ADI Auxiliary Publications Project, Washington 25, D.C.[34]

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(26) All programs used except the least-squares refinement are from the Montana State University Crystallographic Program Library written for the IBM 1620 Model II by C. N. Caughlan, C. T. Li, G. W. Svetich, D. Swank, K. W. Watenpaugh, and R. W. Witters.

(27) "International Tables for Crystallography," Vol. III, The Kynoch Press, Birmingham, England, 1962, pp 202–209.

(28) G. A. Mair, Pure Chemistry Division, National Research Council, Ottawa, Canada, 1963.

(29) These are defined by $\beta = \exp(-\beta_{11}h^2 - \beta_{22}k^2 - \beta_{33}l^2 - \beta_{12}hk - \beta_{23}kl - \beta_{13}hl)$.

(30) The weighting scheme used during the block diagonal refinement was the third form suggested by Mair, *i.e.*, $w = 1/[1 + \{(KF_0 - b)/a\}^2]^{1/2}$, where $a = 8F$ min, $b = 5F$ min, and K = the scale constant.

(31) This refinement was carried out using the University of Washington System Tape for Crystallographic Calculations. The full matrix least-squares refinement program was that of W. R. Busing, K. O. Martin, and H. A. Levy, ORFLS-TM-305, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1962, modified for the University of Washington tape by J. M. Stewart.

(32) The weighting scheme for the last two cycles of refinement was a modified Hughes weighting scheme; see R. D. Willett., C. Dwiggens, Jr., R. Kruh, and R. E. Rundle, *J. Chem. Phys.*, **38**, 2429 (1963). K_1 was chosen as the average intensity for each layer and K_2 as twice the minimum observable intensity.

(33) Least-squares planes are calculated according to the method described by V. Schomaker, S. Waser, R. E. Marsh, and G. Bergman, *Acta Cryst.*, **12**, 600 (1959). The program is one of our library and was written at Montana State University. Each point was given equal weight for these calculations.

(34) A copy of this table may be secured by citing the document number and remitting $1.25 for photoprints or $1.25 for 35-mm microfilm. Advance payment is required. Make checks or money orders payable to Chief, Photoduplication Service, Library of Congress.

Acknowledgment. We thank the National Institutes of Health for Grants GM-8395-06 (C. N. C.) and CA-04769-06 (F. R.), the National Science Foundation for Grant G-19509 (F. R.), and the U. S. Department of Health, Education, and Welfare for an NDEA fellowship (D. S.). We are grateful to the Montana State University and the University of Washington Computing Centers for computing time.

The Structure of 6-Hydroxycrinamine

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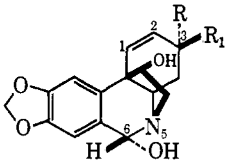
Received July 24, 1967

Abstract: The crystal structure analysis of 6-hydroxycrinamine by X-ray diffraction confirms the stereoconfiguration of the crinamine nucleus as derived from chemical evidence. Furthermore, it establishes that in the solid state the C-6 hydroxyl group is *trans* to the pyrrolidine ring and that the molecules occur as dimers through hydrogen bonding. Eight molecules of $C_{17}H_{19}NO_5$ crystallize in a unit cell of the orthorhombic space group $P2_12_12_1$ with cell dimensions $a = 19.33$, $b = 7.63$, and $c = 21.18$ A. The structure was solved by obtaining a partial structure with phases determined by the symbolic addition procedure and the remainder by a recycling procedure using the tangent formula.

The epimeric alkaloids 6-hydroxycrinamine (Ia) and haemanthidine (Ib), $C_{17}H_{19}NO_5$, are derived from the bulbs of the Amaryllidaceae family. The structures of their 6-deoxy derivatives have been derived from degradative and spectral evidence.[1] On the basis of further chemical and nmr studies it has been suggested that 6-hydroxycrinamine and haemanthidine each exist in solution as a mixture of C-6 epimers.[2] The X-ray diffraction analysis of a crystal of 6-hydroxycrinamine was undertaken to confirm the structure and stereoconfiguration of the crinamine nucleus and to investigate the configuration of the hydroxyl group at C-6.



Ia, $R = H; R_1 = OCH_3$
Ib, $R = OCH_3; R_1 = H$

Crystals of the free base were used. Since the material crystallizes with two molecules in the asymmetric unit, the structure analysis required the location of 184 atoms other than hydrogen atoms in the unit cell of a noncentrosymmetric space group. The structure determination was accomplished in a stepwise fashion. First, several atoms were located from phases determined directly from the magnitudes of the intensities by the symbolic addition procedure as applied to noncentrosymmetric crystals.[3] The remainder of the atoms was found in a recycling procedure using the tangent formula[4] and the partial structure.[5]

Experimental Section

A sample of 6-hydroxycrinamine, obtained from Fales and Wildman from the National Institutes of Health, was recrystallized from a chloroform–cyclohexane mixture. The colorless, platelike crystals were elongated in the *b* direction and could be readily cleaved in the *a* direction. Systematic absences showed the space group to be $P2_12_12_1$. Cell dimensions (A) determined from precession and powder photographs using Cu Kα radiation, $\lambda = 1.5418$ A, are $a = 19.327 \pm 0.010$, $b = 7.634 \pm 0.009$, and $c = 21.184 \pm 0.015$. The density measured with a pycnometer is 1.338 g cm^{-3} while that calculated for eight molecules per cell is 1.349 g cm^{-3}.

Intensity data were collected for seven layers on the *b* axis and four layers on the *a* axis using the multiple-film, equiinclination Weissenberg technique. Although the exposures were of the order of 50 hr, the data did not extend to the limit of the copper sphere. A total of 3521 reflections were recorded. The intensities were estimated visually by comparison with a calibrated film strip. Corrections were made for Lorentz and polarization factors and spot size. Normalized structure factor magnitudes $|E|$ as well as structure factor magnitudes $|F|$ were derived.

Structure Determination

Phase determination was begun with the relation-

$$\phi_{\vec{h}} \approx \langle \phi_{\vec{k}} + \phi_{\vec{h}-\vec{k}} \rangle_{\vec{k}_r} \qquad (1)$$

ship[3] given in (1), where ϕ is the phase and $\vec{h}$ and $\vec{k}$ are the Miller indices, which holds for those reflections with large $|E|$ magnitudes. A measure of the reliability of eq 1 can be obtained by use of the curve of variance, Figure 2 of ref 3b. To implement eq 1, the origin of the cell was specified by assigning phases to three reflections[4] and phases of two additional reflections were specified by the symbols *a* and *b* (see Table I). A total

Table I. Phases Assigned to Implement Eq 1

$\vec{h}$	$\phi_{\vec{h}}$	$\lvert E_{\vec{h}} \rvert$
0 2 7	0	2.63
15 0 4	0	2.97
0 1 5	$+\pi/2$	2.28
9 4 12	a	3.94
7 5 8	b	3.77

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(1) H. M. Fales and W. C. Wildman, *J. Am. Chem. Soc.*, **82**, 197 (1960).

(2) R. W. King, C. F. Murphy, and W. C. Wildman, *ibid.*, **87**, 4912 (1965).

(3) I. L. Karle and J. Karle, *Acta Cryst.*, **17**, 835 (1964); **21**, 849 (1966).

(4) J. Karle and H. Hauptman, *ibid.*, **9**, 635 (1956).

(5) J. Karle, *ibid.*, in press.