CONTRIBUTION FROM THE BEN MAY LABORATORY FOR CANCER RESEARCH AND THE DEPARTMENT OF BIOCHEMISTRY, UNIVERSITY OF CHICAGO]

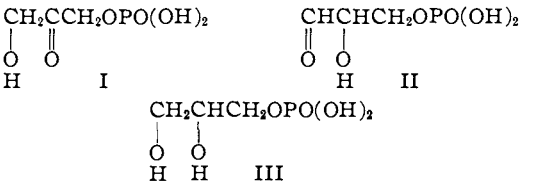
Phosphonic Acids. III.[1] Hydroxyl Substituted Propylphosphonic Acids[2,3]

BY SEYMOUR PREIS, TERRELL C. MYERS AND ELWOOD V. JENSEN

RECEIVED JULY 1, 1955

The peroxide-catalyzed addition of diethyl phosphite to isopropenyl acetate yields diethyl β-acetoxypropylphosphonate, which on hydrolysis gives β-hydroxypropylphosphonic acid. The reaction of triethyl phosphite with epibromohydrin yields diethyl β,γ-epoxypropylphosphonate, which on hydrolysis gives diethyl β,γ-dihydroxypropylphosphonic acid. The biochemical interest in these phosphonic acids as phosphonate analogs of certain phosphorylated intermediates of glycolysis is discussed.

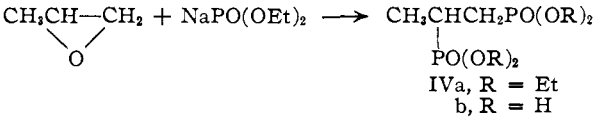
As the glucose molecule enters the living cell it undergoes esterification with phosphoric acid, and in its subsequent metabolic breakdown a large number of the intermediate products react with their respective enzymes in the form of phosphate esters. Typical examples of such phosphorylated intermediates of carbohydrate metabolism include dihydroxyacetone phosphate (I), glyceraldehyde phosphate (II) and α-glycerylphosphate (III). For the most part, the enzymatic transformations of



these and other phosphorylated intermediates do not take place at the phosphate group but at some other point in the molecule. Thus it would seem that the function of the phosphate group in many instances[4] may be to serve as a point of attachment to bind the substrate molecule to the enzyme. If this is true, it is possible that another similar chemical structure, such as the phosphonic acid group, could carry out the same function.

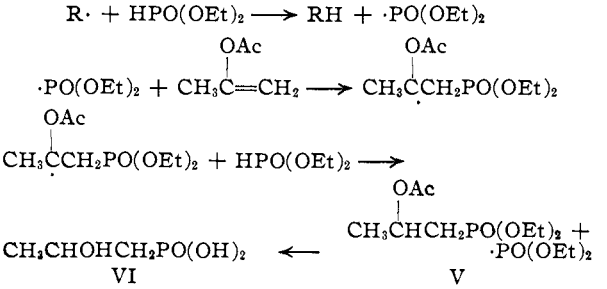
In connection with studies of the mechanism of enzyme–substrate interaction, and in the hope of developing either alternative substrates or else competitive inhibitors for the enzyme systems in question, an investigation of phosphonate analogs of some of these physiologically important phosphate compounds has been undertaken. Such phosphonate analogs of the triose phosphates include both β- and β,γ-substituted propylphosphonic acids, in which the oxygen atom of the phosphate ester is eliminated completely, and γ- and γ,δ-substituted butylphosphonic acids in which the oxygen is replaced by a methylene group. The synthesis of γ-ketobutylphosphonic acid has been reported previously.[1] This paper describes the preparation of β-hydroxypropylphosphonic acid and β,γ-dihydroxypropylphosphonic acid.

It was found that β-hydroxyphosphonic esters could not be prepared by the more common methods for introduction of the phosphonate group. For example, propylene bromohydrin is not converted to diethyl β-hydroxypropylphosphonate by treatment either with triethyl phosphite or with sodium diethyl phosphite. The reaction of propylene oxide with sodium diethyl phosphite led rather unexpectedly to the formation of tetraethyl propyl-1,2-diphosphonate (IVa) which, on acid hydrolysis, is converted to the free propyl-1,2-diphosphonic acid (IVb). In this reaction the primary product may be the expected diethyl β-hydroxypropylphosphonate which undergoes dehydration followed by addition of another molecule of sodium diethyl phosphite to the double bond. The addition of this reagent to a double bond conjugated with a phosphonate group is known to take place readily.[5]



IVa, R = Et
b, R = H

A successful route to β-hydroxyphosphonic acids is afforded by the peroxide-catalyzed addition of diethyl phosphite to an enol ester. Thus a mixture of isopropenyl acetate and diethyl phosphite, when heated in the presence of catalytic amounts of benzoyl peroxide, produces diethyl β-acetoxypropylphosphonate (V) in high yield. Undoubtedly this reaction takes place by a free radical chain mechanism of the general type by which a large variety of substances with labile atoms are known to add to olefins.[6,7] In this process, the initiating radical (R·), formed from the benzoyl peroxide,



(1) Paper II, T. C. Myers, R. G. Harvey and E. V. Jensen, THIS JOURNAL, **77**, 3101 (1955).

(2) Presented before the Division of Organic Chemistry, 123rd Meeting of the American Chemical Society, Los Angeles, March, 1953.

(3) This investigation was supported by grants from the National Institutes of Health, Public Health Service (RG-3053) and from the American Cancer Society as recommended by the Committee on Growth of the National Research Council.

(4) The function of the 6-phosphate group in the metabolic intermediate, fructose 1,6-diphosphate, appears to be the blocking of the 6-hydroxyl group so as to prevent pyranose ring formation; A. L. Lehninger, J. Sicé and E. V. Jensen, *Biochem. Biophys. Acta*, **17**, 286 (1955).

(5) (a) G. Schwarzenbach, P. Ruckstuhl and J. Zurc, *Helv. Chim. Acta*, **34**, 455 (1951); (b) A. N. Pudovik and M. M. Frolova, *Zhur. Obshchei Khim*, **22**, 2052 (1952); *C. A.*, **47**, 9910 (1953).

(6) *Cf.* M. S. Kharasch, E. M. May and F. R. Mayo, *J. Org. Chem.*, **3**, 175 (1938); M. S. Kharasch, E. V. Jensen and W. H. Urry, THIS JOURNAL, **69**, 1100 (1947); A. R. Stiles, F. F. Rust and W. E. Vaughan, *ibid.*, **74**, 3282 (1952).

(7) I. S. Bengelsdorf, Ph.D. Dissertation, University of Chicago, 1951.

abstracts the labile hydrogen atom from a molecule of diethyl phosphite to form a diethylphosphoryl radical which then adds to the double bond of isopropenyl acetate. The free radical thus formed then may undergo one of two possible reactions. It may abstract an atom of hydrogen from diethyl phosphite to yield the desired product V and a new diethylphosphoryl radical which carries on the reaction chain. Alternatively, it may add to another molecule of isopropenyl acetate to give a free radical containing two residues of isopropenyl acetate per phosphonate group; this radical then may react either with diethyl phosphite to give a 2:1 addition product or with still another isopropenyl acetate molecule, and so on. When the reaction is carried out with equal molar amounts of diethyl phosphite and isopropenyl acetate, the intermediate radicals apparently react in both possible ways, so that a considerable amount of the product contains two or more residues of isopropenyl acetate per phosphonate group. However, when the reaction is carried out in a 2.5-fold excess of diethyl phosphite as solvent, the intermediate radicals react preferentially with this material; under these conditions 72% of the isopropenyl acetate is converted to the 1:1 addition product while only 16% appears in the products of higher molecular weight

Upon warming the acetoxyphosphonic ester V with hydrochloric acid, hydrolytic cleavage of the acetate as well as the phosphonate ester linkages takes place to yield β-hydroxypropylphosphonic acid (VI), an oily liquid which was isolated as its crystalline cyclohexylamine salt.

For the preparation of β,γ-dihydroxypropylphosphonic acid (VIII) a convenient starting material was found to be diethyl β,γ-epoxypropylphosphonate (VII) prepared as described previously[7,8] by the reaction of triethyl phosphite with epibromohydrin. When diethyl epoxypropylphosphonate is warmed in excess water

$$\underset{\text{VII}}{CH_2CHCH_2PO(OEt)_2} \xrightarrow{H_2O} \underset{\text{VIII}}{CH_2OHCHOHCH_2PO(OH)_2}$$

hydrolytic cleavage of both the epoxide ring and the phosphonate ester groups takes place to yield dihydroxypropylphosphonic acid (VIII), a sirupy liquid which was isolated in the form of its barium salt.

Investigations of the effects of the foregoing propylphosphonic acids on various biochemical systems *in vitro* and *in vivo* will be described in subsequent publications.

Experimental

Materials.—Diethyl phosphite and triethyl phosphite were obtained from the Virginia–Carolina Chemical Company. These materials, as well as all liquid organic reagents, were purified by distillation prior to use. Tetrahydrofuran (du Pont) was allowed to stand with several fresh portions of solid potassium hydroxide and then distilled from sodium ribbon.

Tetraethyl Propyl-1,2-diphosphonate (IVa).—A stirred solution of sodium ethoxide (77 g., 1.14 moles) and diethyl phosphite (157 g., 1.14 moles) in tetrahydrofuran (400 ml.) was warmed to reflux, and propylene oxide (66 g., 1.14 moles) was added slowly causing the formation of a white precipitate. The addition of propylene oxide was complete in one hour, whereupon the cooled reaction mixture was neutralized by pouring it through a column containing Amberlite IRC-50H resin (350 g.) which had been washed previously with absolute alcohol. After removal of the tetrahydrofuran, the residue was fractionated at reduced pressure. The major fractions (39 g., b.p. 120–170° (0.3 mm.)) showed a nearly constant refractive index; a high boiling residue (19 g.) remained. Redistillation of the combined major fractions gave tetraethyl propyl-1,2-diphosphonate (35.5 g., 22%; b.p. 120–148° (0.3 mm.), $n^{25}D$ 1.4400). A portion of this material was distilled through a Podbielniak Heliband micro-column to obtain the analytical sample; b.p. 133° (0.9 mm.), $n^{25}D$ 1.4406; reported[5b] b.p. 160–162° (3 mm.), $n^{20}D$ 1.4430.

Anal. Calcd. for $C_{11}H_{26}O_6P_2$: C, 41.77; H, 8.29; P, 19.59. Found: C, 41.53; H, 8.53; P, 19.72.

Propyl-1,2-diphosphonic Acid[9] (IVb).—A 2-g. portion of the column-distilled tetraethyl propyl-1,2-diphosphonate (IV) was refluxed overnight with 20 ml. of concentrated hydrochloric acid. The solution was then evaporated *in vacuo*. After several days the oily residue crystallized. Several recrystallizations of this material from *t*-butyl alcohol yielded propyl-1,2-diphosphonic acid, m.p. 123°.

Anal. Calcd. for $C_3H_{10}O_6P_2$: C, 17.65; H, 4.94; P, 30.36; neut. equiv. (to *p*H 4.5), 102. Found: C, 17.93; H, 5.08; P, 30.64; neut. equiv., 104.

Diethyl β-Acetoxypropylphosphonate (V).—A solution of benzoyl peroxide (5 g.) in isopropenyl acetate (93 g., 0.93 mole) was added slowly to a stirred solution of diethyl phosphite (319 g., 2.3 mole) held at 85 to 95°. When the addition was complete (3 hours) a further 5-g. quantity of benzoyl peroxide was added and heating continued for another hour. Then the excess diethyl phosphite was removed under reduced pressure. The residual oil was distilled, and the fraction boiling at 78–100° (0.5 mm.) was redistilled yielding diethyl β-acetoxypropylphosphonate, b.p. 89–93° (0.5 mm.), $n^{25}D$ 1.4301. The yield was 160 g., 72%.

Anal. Calcd. for $C_9H_{19}O_5P$: C, 45.37; H, 8.04; P, 13.00. Found: C, 45.44; H, 8.26; P, 12.96.

The higher boiling fractions contained about 25 g. of a substance containing two residues of isopropenyl acetate to one of diethyl phosphite (b.p. 100–115° (0.1 mm.), $n^{25}D$ 1.4461).

When the reaction was carried out using equal molar proportions of diethyl phosphite and isopropenyl acetate, the yield of 1:1 product was only 35%, and the amount of higher boiling material was markedly increased. In this case the latter material, after molecular distillation, consisted mainly of an adduct containing three isopropenyl acetate molecules per diethyl phosphite ($n^{25}D$ 1.4523).

Anal. Calcd. for $C_{19}H_{35}O_9P$: C, 52.04; H, 8.05; P, 7.07. Found: C, 51.78; H, 7.96; P, 9.06.

β-Hydroxypropylphosphonic Acid (VI).—Diethyl β-acetoxypropylphosphonate (V, 4.5 g., 0.019 mole) was warmed overnight on the steam-bath with concentrated hydrochloric acid (10 ml.). The reaction mixture was evaporated in a stream of nitrogen and finally *in vacuo* leaving β-hydroxypropylphosphonic acid as a brownish sirup. This material was dissolved in water, and the solution was decolorized with Norit. To the colorless solution was added cyclohexylamine (1.77 g., 0.018 mole). The mixture was concentrated to about 3 ml.; a small amount of precipitate was removed by centrifugation, and the supernatant solution was concentrated to a small volume. The precipitated solid was removed by filtration, washed with a little cold isopropyl alcohol and recrystallized several times from a mixture of ethanol and tetrahydrofuran. The monocyclohexylamine salt of β-hydroxypropylphosphonic acid was obtained as white lustrous needles, m.p. 194–196° with decomposition.

Anal. Calcd. for $C_9H_{22}O_4NP$: C, 45.17; H, 9.27; N,

(8) *Cf.* B. A. Arbuzov and B. P. Lugokvin, *Zhur. Obshchei. Khim.*, **22**, 1193 (1952); *C. A.*, **47**, 4871 (1953), for preparation from epiiodohydrin.

(9) Propyl-1,2-diphosphonic acid has been described previously[5a] as a non-crystalline material. Our propyldiphosphonic acid (m.p. 123°) has been assigned this structure since it is not propyl-1,3-diphosphonic acid (m.p. 172°, P. Nylen, Dissertation, Uppsala, 1930) and the possibility that it is propyl-1,1-diphosphonic acid seems unlikely.

5.85; P, 12.95. Found: C, 45.47; H, 9.60; N, 6.14; P, 13.20.

Diethyl β,γ-Epoxypropylphosphonate (VII).—Triethyl phosphite (332 g., 2.0 moles) was added slowly with stirring to epibromohydrin (261 g., 2.0 mole) held at 135–145°. The addition was complete in four hours and heating and stirring was continued for two hours longer. During the reaction the ethyl bromide produced (169 g., 1.55 moles) was removed continuously by a gentle stream of nitrogen. On distillation of the reaction mixture, the main fraction (197 g., 51% yield) consisted of diethyl epoxypropylphosphonate, b.p. 68–72° (0.1 mm.); $n^{25}D$ 1.4379; reported $n^{20}D$ 1.4430,[7] 1.4405.[8]

Anal. Calcd. for $C_7H_{15}O_4P$: C, 43.30; H, 7.79; P, 16.00. Found: C, 42.59; H, 7.99; P, 15.93.

The high boiling residue from the above reaction mixture (72 g.) was molecularly distilled at about 95°. The main portion of this distillate ($n^{25}D$ 1.4549) appeared to possess approximately two phosphonate units per propane residue.

Anal. Found: C, 40.00; H, 7.18; P, 19.4.

β,γ-Dihydroxypropylphosphonic Acid (VIII).—Diethyl β,γ-epoxypropylphosphonate (VII) was placed in water and warmed on the steam-bath. The oil gradually dissolved and the solution became acidic. After heating for six days, the water was removed at reduced pressure leaving the dihydroxypropylphosphonic acid as a viscous sirup ($n^{25}D$ 1.4971) which could not be completely freed of water, but which was isolated in the form of its barium salt by the procedure of Arbuzov and Lugovkin[8] and recrystallized from water.

Anal. Calcd. for $C_6H_{16}O_{10}P_2Ba$: P, 13.85; Ba, 30.69. Found: P, 13.30, 13.10; Ba, 31.15, 31.44.

CHICAGO 37, ILLINOIS

[CONTRIBUTION FROM THE CHEMISTRY RESEARCH BRANCH, AERONAUTICAL RESEARCH LABORATORY, WRIGHT AIR DEVELOPMENT CENTER]

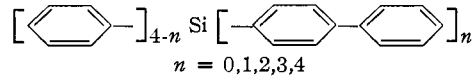
Organo-silicon Chemistry. I. The Mixed Phenyl- and *p*-Biphenylyl-substituted Silanes, their Physical Properties and Infrared Absorption Spectra[1]

BY LEONARD SPIALTER, DAVID C. PRIEST AND CHARLES W. HARRIS

RECEIVED APRIL 1, 1955

Triphenyl-*p*-biphenylylsilane, diphenyl-di-*p*-biphenylylsilane, phenyltri-*p*-biphenylylsilane and tetra-*p*-biphenylylsilane have been synthesized in 80–90% yields by modified Wurtz reactions between appropriate phenylchlorosilanes and *p*-bromobiphenyl with sodium in ether. Melting and boiling points and solubility data for these compounds and for tetraphenylsilane are tabulated and discussed. Infrared absorption spectra are presented and pertinent structure–spectra correlations are analyzed.

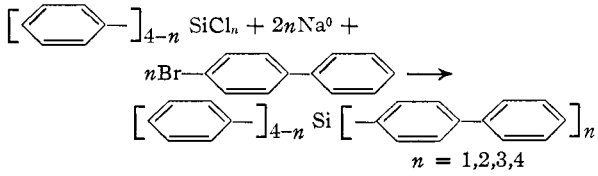
It is of interest to investigate types of organic compounds which promise unusual thermal stability coupled with low vapor pressure. One class of such compounds comprises completely arylated silicon compounds. In the present paper are described the syntheses and properties of some members of one subclass in this category, namely, the tetraarylmonosilanes wherein the aryl substituents are phenyl and *p*-biphenylyl. These compounds can be expressed by the general formula as



n = 0,1,2,3,4

Previously the only members of this last group which had been reported were tetraphenylsilane[2,3] and tetra-*p*-biphenylylsilane.[3,4] To help resolve the confusion which exists with respect to the simple physical properties of these compounds and to investigate the behavior of the intermediate members of this series, the entire series has been prepared and its characteristics studied.

The basic synthetic method is essentially a modified Wurtz reaction wherein the appropriate chlorosilane and chlorobenzene or *p*-bromobiphenyl are condensed with sodium in ether. The desired product is isolated by evaporation of the reaction mixture to dryness followed by solvent extraction. Yields are of the order of 80–90%. The general preparative reaction for the biphenylylsilanes is



n = 1,2,3,4

Since thermal stability and low vapor pressures are important attributes in this class of compounds, a small apparatus was designed for the rough determination of boiling points at atmospheric pressure in the temperature range from about 400 to 750°.

Experimental Part[5]

Tetraphenylsilane (I).—The method of Polis[6] was used. The product, recrystallized from benzene and further purified by sublimation, consisted of long thin needles, m.p. 236.5–237° (lit. m.p. 234°[7]).

Anal. Calcd. for $C_{24}H_{20}Si$: C, 85.67; H, 5.99; Si, 8.34. Found: C, 85.20, 85.53; H, 5.90, 6.17; Si, 8.31, 8.36.

Tetra-*p*-biphenylylsilane (II).—A modification of the Polis[6] method was used. Into a 500-ml. 3-neck flask, equipped with a mercury-sealed stirrer and condenser protected by a calcium chloride tube, were placed 10.8 g. (0.046 mole) of *p*-bromobiphenyl, 1.95 g. (0.0116 mole) of silicon tetrachloride and 100 ml. of anhydrous ether. To this solution was added 2.5 g. (0.11 gram atom) of sodium ribbon. The mixture was heated to reflux temperature and stirred for about 4 hours when nearly all of the sodium had reacted. The ether was then distilled and the residue was extracted

(1) Presented before the Division of Organic Chemistry, 124th Meeting of the American Chemical Society, Chicago, Ill., September, 1953.

(2) See references in H. W. Post, "Silicones and Other Organic Silicon Compounds," Reinhold Publ. Corp., New York, N. Y., 1949, p. 187.

(3) E. G. Rochow, "Chemistry of the Silicones," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1951, p. 172.

(4) Reference 2, p. 188.

(5) All melting points are corrected and were determined with a Kofler micro hot-stage with a heating rate of about 2° per minute at the melting point. Microanalyses were performed by Oakwold Laboratories, Alexandria, Va.

(6) A. Polis, *Ber.*, **18**, 1541 (1885); **19**, 1013 (1886).

(7) S. Sugden and H. Wilkins, *J. Chem. Soc.*, 126 (1931).