

ately neutralized³⁴ to pH 7.5 with calcium hydroxide. The solution was then concentrated to about 4 ml. (check pH), filtered to remove impurities and the product precipitated by adding three volumes of ethanol. The precipitate was collected by centrifugation, washed with alcohol and acetone and dried *in vacuo*.

(D) **Ribonucleoside-5' Phosphates.**—The methods for the preparation of the P³²-labeled ribonucleoside-5' phosphates are analogous to those described above in the deoxyribonucleoside series. However, the readily available isopropylidene derivatives have been used to prevent reaction with the 2'- and 3'-hydroxyl groups. The tabulated proportions of reactants have been used. The nucleoside and

For 1 mmole of nucleoside	2-Cyanoethyl phosphate, mmole	DCC, mmoles
Isopropylideneuridine ^a	0.5	2.0
Benzylidencytidine	1.0	4
Isopropylideneadenosine ^a	0.65	3.0
Isopropylidene-guanosine ^a	0.6	2.5

^a Aldrich Chemical Co. Inc., 2369 N. 29th St., Milwaukee 10, Wis.

(34) The product is chromatographically and electrophoretically pure. For most purposes this solution can be neutralized (pH 7), concentrated to a convenient volume and used directly.

the 2-cyanoethyl phosphate were dried by repeated evaporation with dry pyridine in the usual manner and then dissolved in 0.5 ml. of dry pyridine and the DCC added. After 20 hours at 25°, the well-stoppered flask was opened and 1 ml. of water added. After an hour the solution was concentrated to dryness *in vacuo*. The residue was hydrolyzed 90 minutes in 10% acetic acid (40 ml.) at 100° to remove the isopropylidene group and cleave phosphoamide bonds. The acetic acid was then removed by evaporating the solution to dryness with last traces being removed by a second evaporation after adding 10 ml. of water. The residue was next heated with 40 ml. of 9 N ammonium hydroxide at 60° for 90 minutes and the ammonia removed by concentrating the mixture to dryness. Ten ml. of water was added to the residue and the insoluble dicyclohexylurea removed by filtration. The precipitate was well washed with water. The nucleotides were isolated from the filtrate in 40–60% yield by ion exchange chromatography^{36a,b} on Dowex 1 resin, by preparative paper chromatography on Whatman 3MM paper in solvent A or by barium salt precipitation.

Acknowledgments.—I would like to thank Dr. P. Townsley for his help in the synthesis of P³²-labeled nucleotides.

(35) (a) W. E. Cohn, *THIS JOURNAL*, **72**, 1471, 2811 (1950); (b) W. E. Cohn and J. X. Khyrn, in Shemin, "Biochemical Preparations," Vol. 5, John Wiley and Sons, Inc., New York, N. Y., 1957, pp. 40–48.

[CONTRIBUTION FROM THE STAMFORD LABORATORIES, CHEMICAL RESEARCH DEPARTMENT, CENTRAL RESEARCH DIVISION, AMERICAN CYANAMID CO., STAMFORD, CONN.]

Reactions of Phosphine with Aliphatic Aldehydes¹

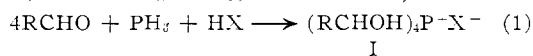
BY SHELDON A. BUCKLER AND V. P. WYSTRACH

RECEIVED AUGUST 8, 1960

The reaction of phosphine with aliphatic aldehydes in aqueous mineral acid solution has been found to be quite useful as a method of C–P bond formation. The nature of the product varies considerably with different types of aldehydes. Of particular interest are spiro-phosphonium salts obtained from dialdehydes and derivatives of 1,3-dioxo-5 phosphacyclohexane obtained from α -branched aldehydes. *n*-Alkyl aldehydes give tetrakis-(1-hydroxyalkyl)-phosphonium salts, and chloral and dichloroacetaldehyde give 1-hydroxyalkyl secondary phosphines. A study of possible catalysts other than aqueous mineral acid is also reported.

Introduction

Relatively few publications have appeared in the literature describing the addition of phosphine to carbonyl groups. The most comprehensive study is that of Messinger and Engels who examined the reaction of phosphine with several aldehydes and ketones in ether solution using anhydrous HCl or HBr as catalyst.² Acetaldehyde and propionaldehyde reacted readily to give tetrakis-(1-hydroxyalkyl)-phosphonium halides as the major products (eq. 1, R = CH₃, C₂H₅; X = Cl, Br). In addition,



tion, oils were usually obtained which appeared to be tertiary phosphine hydrohalides of the type (RCHOH)₃P·HX. Isobutyraldehyde and acrolein gave uncharacterized sirupy masses as products under these conditions.

More recently, attention has been directed to the reactions of formaldehyde and phosphine. Excellent yields of tetrakis-(hydroxymethyl)-phosphonium chloride have been obtained from reactions carried out in concentrated aqueous HCl.^{3,4}

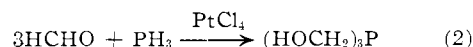
(1) A preliminary report of portions of this work has been published: S. A. Buckler and V. P. Wystrach, *THIS JOURNAL*, **80**, 6454 (1958).

(2) J. Messinger and C. Engels, *Ber.*, **21**, 326, 2919 (1888).

(3) A. Hoffman, *THIS JOURNAL*, **43**, 1684 (1921).

(4) W. A. Reeves, F. F. Flynn and J. D. Guthrie, *ibid.*, **77**, 3923 (1955).

The use of a metal salt as catalyst has led to faster reactions and, in the absence of acid, to a product of lesser aldehyde addition, tris-(hydroxymethyl)-phosphine.⁵



Although nothing further appears in the literature relating to the reactions of phosphine with aliphatic aldehydes, certain reactions observed with phosphonium iodide in non-aqueous media will be cited here since these may well proceed by addition of phosphine rather than phosphonium ion. De Girard studied these reactions and found that tetrakis-(1-hydroxyalkyl)-phosphonium iodides and some lower substitution products were obtained from *n*-alkyl aldehydes.⁶ In addition, he found that chloral and trichlorobutyraldehyde gave crystalline derivatives which probably have the structures (CCl₃CHOH)₂PH and (CH₃CHClCCl₂CHOH)₂PH, respectively.

Recent reports from this Laboratory have described the reactions of phosphine with ketones⁷ and aromatic aldehydes⁸ which differ from those observed with aliphatic aldehydes in that transfer

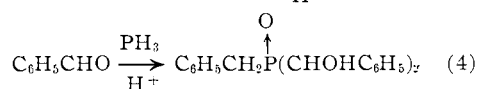
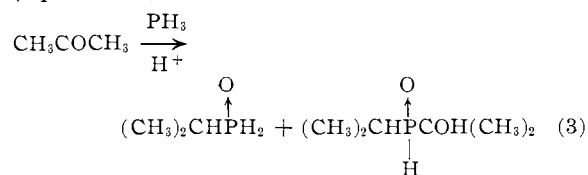
(5) M. Reuter, U. S. Patent 2,912,466 (1959); M. Reuter and L. Orthner, German Patent 1,035,135 (1958).

(6) M. A. De Girard, *Ann. chim.*, [6] **2**, 11 (1884).

(7) S. A. Buckler and M. Epstein, *THIS JOURNAL*, **82**, 2076 (1960).

(8) S. A. Buckler, *ibid.*, **82**, 4215 (1960).

of oxygen from carbon to phosphorus takes place (eq. 3 and 4).



Results and Discussion

Most of the reactions of phosphine and aliphatic aldehydes studied previously were carried out in non-aqueous media and mixtures of products were usually obtained. In view of the potential of this reaction as a method of C-P bond formation, an investigation of other means of effecting this carbonyl addition was undertaken. Most aliphatic aldehydes were found to react cleanly with phosphine in aqueous mineral acid solution and an interesting array of products has been observed, since the reaction course varied with different types of aldehydes.

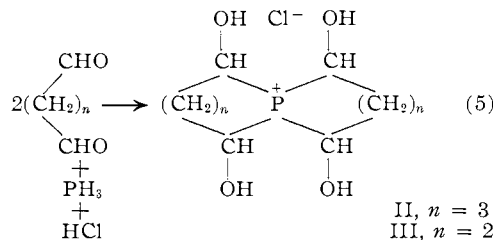
***n*-Alkyl Aldehydes.**—The procedure used previously in preparing tetrakis-(hydroxymethyl)-phosphonium chloride (I, R = H, X = Cl) consisted of passing phosphine into a mixture of aqueous formaldehyde and HCl.^{3,4} It has now been found that under suitable conditions phosphine will react with *n*-alkyl aldehydes, even when long chains are present, to give phosphonium salts in 98–100% yield; salts have been prepared from acetaldehyde, heptanal and dodecanal (I, R = CH₃, *n*-C₆H₁₃, and *n*-C₁₁H₂₃; X = Cl).

It was found advantageous to add the aldehyde slowly to the reaction mixture to suppress acid-catalyzed condensations. Also, the presence of an organic diluent such as tetrahydrofuran is desirable to increase the solubility of phosphine and the higher aldehydes. One experiment conducted with a mole ratio of heptanal to HCl of 10:1 gave a quantitative yield of the corresponding phosphonium salt based on HCl as the limiting reagent. Thus, greater than stoichiometric amounts of acid need not be employed.

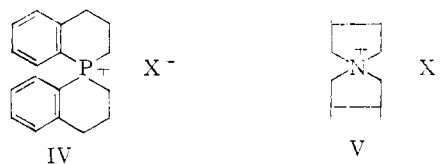
It is interesting to note that with these experimental conditions, the tetrasubstituted product is formed exclusively although excess phosphine usually was present. With heptanal and dodecanal, appearance of the insoluble phosphonium salt was noted immediately upon adding the first drops of aldehyde to the phosphine-saturated reaction mixture. Apparently reactivity toward aldehydes increases in the series PH₃ < RCH₂OHPH₂ < (RCHOH)₂PH < (RCHOH)₃P. This phenomenon is in accord with the reported increases in basicity and nucleophilicity which occur upon successive replacement of the hydrogens of phosphine with alkyl groups.^{9–11} The tendency for this reaction to be arrested in part at the tertiary phosphine stage in ether solution due to

interaction with acid² is not observed in an aqueous medium.

Dialdehydes.—It has been found that dialdehydes which can form relatively stable five- and six-membered rings react readily with phosphine to give spirocyclic phosphonium salts. Glutaraldehyde gave a 65% yield of 1,5,7,11-tetrahydroxy-6-phosphoniaspiro[5.5]undecane chloride (II), and succinaldehyde gave a 34% yield of 1,4,6,9-tetrahydroxy-5-phosphoniaspiro[4.4]nonane chloride (III). Attempts to prepare an analogous spiran

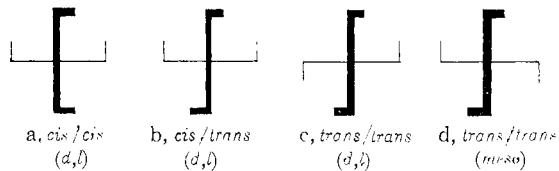


by reaction with glyoxal were unsuccessful. The only spiran reported previously in which the spiro atom is tetravalent phosphorus and other atoms comprising the rings are carbon is IV, which was prepared by Hart and Mann¹² using a lengthy synthesis.



It is felt that the reaction of dialdehydes with compounds having P-H bonds holds considerable promise as a method of preparing phosphorus heterocycles. Furthermore, the hydroxyl groups could serve as useful "handles" for modification of the rings.

The stereochemistry of the spirans II and III is interesting. A related case has been studied carefully by McCasland and Proskow who examined the stereoisomers of 2,3,7,8-tetramethyl-5-azoniaspiro[4.4]nonane *p*-toluenesulfonate (V).¹³ Since the spiro nitrogen atom is tetrahedral, the four possible diastereomers were described conveniently by the diagrams a-d in which the intersecting lines describe the planes of the rings and the shorter, non-intersecting lines represent the orientation of the methyl groups.¹³ Three of the



diastereomers, a-c, were racemic, b and c being obtained in optically active forms. The fourth diastereomer was found to be *meso* although it has neither a plane nor a center of symmetry. This substance is *meso* by virtue *only* of a fourfold alternating axis of symmetry, and the work of Mc-

(9) H. C. Brown, *THIS JOURNAL*, **67**, 503 (1945).

(10) W. A. Henderson, Jr., and C. A. Streuli, *ibid.*, **82**, 5791 (1960).

(11) W. A. Henderson, Jr., and S. A. Buckler, *ibid.*, **82**, 5794 (1960).

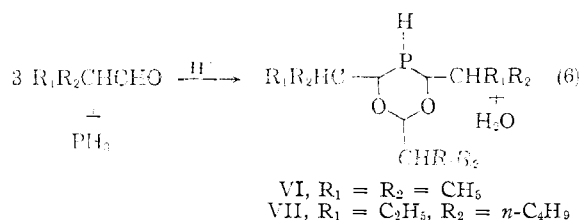
(12) F. A. Hart and F. G. Mann, *J. Chem. Soc.*, 4107 (1955).

(13) G. E. McCasland and S. Proskow, *THIS JOURNAL*, **77**, 4688 (1955); **78**, 5646 (1956).

Casland and Proskow provided the first experimental verification of this phenomenon.

The possible diastereomers of the spirocyclic phosphonium salts II and III may also be represented by diagrams a-d in which the non-intersecting lines designate hydroxyl groups. However, these substances are fundamentally different from V in that the substituents are on carbon atoms adjacent to the spiro atom. Examination of the molecular models of II and III indicated that d was the most favorable form since it was the only one of the four possibilities in which hydroxyl groups from different rings do not interfere with each other. This is particularly evident in III, the spiran which has five-membered rings. Therefore, the reaction of phosphine and succinaldehyde might well be stereospecific, leading to the isomer of III having the stereochemistry indicated in d. Attempts to gain chemical evidence bearing on this point have not been fruitful.

α -Branched Aldehydes.—Aldehydes which are branched at the α -position would not be expected to form hydroxylalkyl phosphonium salts (I) because of steric repulsion among the substituent groups. These aldehydes have been found to react rapidly with phosphine in aqueous HCl to give secondary phosphines in which the phosphorus is part of a novel heterocyclic system (eq. 6). Isobutyraldehyde gave a 75% yield of 2,4,6-trisopropyl-1,3-dioxo-5-phosphacyclohexane (VI) and 2-ethylhexanal gave a 90% yield of 2,4,6-(3-heptyl)-1,3-dioxo-5-phosphacyclohexane (VII).

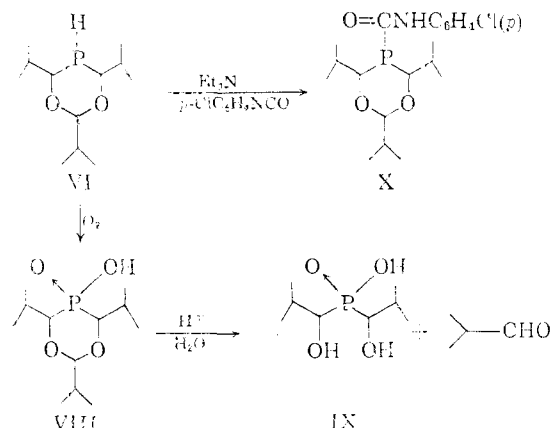


Presumably only two C-P bonds are formed in these reactions because of steric hindrance toward further phosphine-aldehyde reaction in the di-substituted intermediates, $(R_1R_2CHOH)_2PH$. The reason for subsequent acetal formation under these conditions is not immediately obvious since the hydroxyl groups should also be hindered toward reaction with aldehyde. However, the explanation may lie in the tendency of bulky substituents to accelerate ring closure and retard hydrolytic ring opening.¹⁴ It was found that a suspension of VI in concentrated hydrochloric acid could be boiled for two hours without appreciable hydrolysis.

The secondary phosphines VI and VII are stable liquids which, unlike typical dialkyl phosphines, have a mild, not-unpleasant odor. They are also more stable toward atmospheric oxygen than most other secondary phosphines. Typical P-H infrared absorption at 2300 cm^{-1} was observed in these compounds. These materials are particularly attractive since other reactions leading to secondary phosphines in high yield which would be suitable for large scale preparations are rare.

(14) F. G. Bordwell, C. E. Edwards and R. D. Chapman, *THIS JOURNAL* **81**, 2698 (1959).

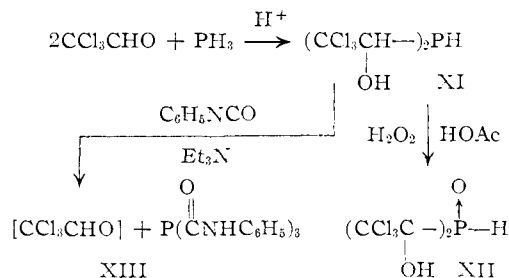
Treatment of VI with air in boiling 2-propanol gave the phosphinic acid VIII. Hydrolysis of the acetal linkage in this acid gave isobutyraldehyde and bis-(1-hydroxy-2-methylpropyl)-phosphinic acid (IX). Reaction of VI with *p*-chlorophenyl isocyanate gave the carbamoyl derivative X.



The reaction of phosphine and 2-phenylpropanal ($R_1 = \text{C}_6\text{H}_5, R_2 = \text{CH}_3$) did not lead to a cyclic secondary phosphine. Instead, a glass-like material was formed which gave a small amount of crystalline solid when treated with hydrogen peroxide (see Experimental).

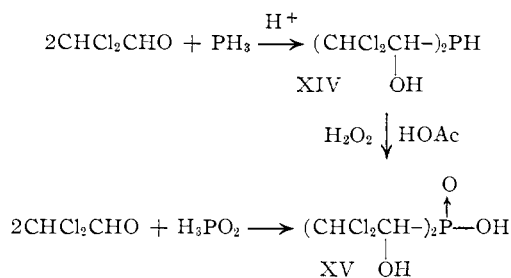
α -Chloro Aldehydes.—Phosphine reacts smoothly with chloral in aqueous hydrochloric acid solution to give bis-(2,2,2-trichloro-1-hydroxyethyl)-phosphine (XI) in 95% yield. This product was obtained previously by De Girard from the reaction of phosphonium iodide and chloral.⁶

Although XI showed no P-H absorption in the infrared in a Nujol mull and only very weak absorption at 2370 cm^{-1} in tetrahydrofuran solution, there can be little doubt that the indicated structure is the correct one in view of the following evidence. The phosphorus n.m.r. spectrum showed a 1-1 doublet centered at +43 p.p.m. (relative to 85% H_3PO_4) with a splitting of 14 p.p.m., which is reasonable for this type of secondary phosphine. Treatment of XI with hydrogen peroxide in acetic acid gave bis-(2,2,2-trichloro-1-hydroxyethyl)-phosphine oxide (XII) with normal P-H absorption at 2400 cm^{-1} . Reaction of phenyl isocyanate with XI in the presence of triethylamine gave tris-(phenylcarbamoyl)-phosphine (XIII) which has been reported previously as the product of the reaction of phosphine and phenyl isocyanate.¹⁵ Thus, the reaction of phosphine and chloral is reversible.



(15) S. A. Buckler, *J. Org. Chem.*, **24**, 1460 (1959).

Reaction of phosphine with dichloroacetaldehyde gave bis-(2,2-dichloro-1-hydroxyethyl)-phosphine (XIV). This material was troublesome to purify and was converted to bis-(2,2-dichloro-1-hydroxyethyl)-phosphinic acid (XV) for characterization. Independently, XV was prepared by reaction of dichloroacetaldehyde and hypophosphorous acid.



Chloroacetaldehyde reacted with phosphine in 3:1 molar ratio to give an amorphous solid which could neither be purified nor converted successfully to suitable derivatives. The α -chloro aldehydes may give products with phosphine which contain fewer aldehyde units than those obtained from *n*-alkyl aldehydes because of either steric or electronic factors, or both.

Investigation of Catalysts.—The reactions of phosphine with various aldehydes which have been described in this paper were carried out in the presence of aqueous mineral acid as catalyst. Some results obtained with other catalysts are also worth reporting.

Heptanal failed to react significantly with phosphine at room temperature in the absence of any added catalyst or in the presence of aqueous potassium hydroxide. Similarly, attempts to react phosphine and isobutyraldehyde in the gas phase in the presence of a silica-alumina catalyst at temperatures up to 375° did not give promising results. At higher temperatures the phosphine was decomposed to white phosphorus and hydrogen.

Reaction of phosphine and heptanal in the presence of aluminum chloride gave a pyrophoric mixture of 1-hydroxyheptylphosphines which was not readily separated by distillation because of the tendency of these materials to revert to heptanal and phosphine upon heating. Air oxidation gave crystalline tris-(1-hydroxyheptyl)-phosphine oxide in 34% yield.

Thus, products containing a lesser number of alkyl groups can be obtained from the reaction of phosphine and aldehydes by the use of aluminum chloride and other metallic catalysts⁵ rather than aqueous mineral acid. This, taken together with the variety of products which can be obtained under the aqueous mineral acid conditions through the use of the different types of aldehydes, demonstrates that the phosphine-aldehyde reaction has considerable value in the synthesis of organophosphorus compounds.

Acknowledgments.—Some of the experiments with chloro aldehydes were carried out by Mr. Martin Epstein. Microanalyses were carried out under the supervision of Dr. J. A. Kuck and Mrs. E. C. Grim.

Experimental¹⁶

Phosphine was allowed to react with aldehydes by two different experimental methods. Method A consisted of adding gaseous phosphine and the liquid aldehyde simultaneously into a Morton flask which contained the reaction solvent. Vigorous stirring was employed and sufficient phosphine was passed in to maintain a slow exit stream through a terminal bubbler. In method B, a solution of the aldehyde and solvent was prepared in a pressure bottle and treated with phosphine in a standard Parr pressure reaction apparatus under 1–4 atmospheres of phosphine. Detailed descriptions of these methods can be found in previous publications from this Laboratory.^{8,15,17}

Tetrakis-(1-hydroxyethyl)-phosphonium Chloride (Method A).—A solution of 132 g. (3.0 moles) of acetaldehyde in 100 ml. of water was added to a solution of 310 ml. of concentrated HCl and 200 ml. of tetrahydrofuran in the course of 1.5 hours while maintaining phosphine saturation and vigorous stirring. The temperature was maintained at 20–30° by external cooling. The resulting solution was evaporated *in vacuo* and the residue dried in a desiccator to give 181 g. (98%) of product, m.p. 110–113°. Thorough trituration with cold acetonitrile gave a purer material, m.p. 115–116°. A m.p. of 112° was reported previously.²

Tetrakis-(1-hydroxyheptyl)-phosphonium Chloride (Method A).—To a solution of 300 ml. of concentrated HCl and 300 ml. of tetrahydrofuran was added 161 g. (1.4 moles) of heptanal over a period of 1.8 hours while maintaining a temperature of 20–25°. Precipitation of solid began immediately. The product was collected by filtration and air-dried to give 185 g. (100%) of material in the form of a white powder, m.p. 114–118°. The analytical sample was prepared by recrystallization from benzene, m.p. 123–124°.

Anal. Calcd. for C₂₈H₆₀ClO₄P: C, 63.79; H, 11.47; Cl, 6.73; P, 5.88. Found: C, 63.48; H, 11.38; Cl, 6.47; P, 5.67.

Tetrakis-(1-hydroxydodecyl)-phosphonium Chloride (Method A).—To a solution of 200 ml. of concentrated HCl and 250 ml. of tetrahydrofuran was added 59 g. (0.32 mole) of dodecanal. Precipitation of solid began immediately. The product was collected by filtration in the form of small, waxy, white beads. There was obtained 64.5 g. (100%) of material, m.p. 106–107°, after drying *in vacuo*. The m.p. was raised to 109–110° by recrystallization from 1:1 benzene-ethyl acetate.

Anal. Calcd. for C₄₈H₁₀₀ClO₄P: C, 71.37; H, 12.48; Cl, 4.39; P, 3.84. Found: C, 71.12; H, 12.51; Cl, 4.49; P, 4.18.

1,5,7,11-Tetrahydroxy-6-phosphoniaspiro[5.5]undecane Chloride (II) (Method A).—To a mixture of 225 ml. of tetrahydrofuran and 125 ml. of concentrated HCl was added 268 g. (0.67 mole) of a 25% aqueous solution of glutaraldehyde in the course of 2 hours while maintaining a temperature of 20–30°. The resulting solution was filtered to remove traces of suspended solid and evaporated *in vacuo*. The residue was triturated with acetone, filtered, and dried to give 59 g. (65%) of II, m.p. 166–167° dec. This was recrystallized from *sec*-butyl alcohol to give the analytical sample, m.p. 167–168° dec.

Anal. Calcd. for C₁₀H₂₀ClO₄P: C, 44.37; H, 7.45; Cl, 13.10; P, 11.44; mol. wt./2, 135.4. Found: C, 44.51; H, 7.55; Cl, 13.07; P, 11.58; mol. wt., 131.3 (cryoscopic in water¹⁸).

1,4,6,9-Tetrahydroxy-5-phosphoniaspiro[4.4]nonane Chloride (III) (Method A).—To a solution of 200 ml. of tetrahydrofuran and 200 ml. of concentrated HCl was added 107 g. (0.67 mole) of 2,5-diethoxytetrahydrofuran¹⁹ in the course of 2.2 hours while maintaining a temperature 25–30°. The resulting solution was evaporated *in vacuo* and the residual gum partly crystallized after standing for several days. To this was added 150 ml. of amyl alcohol and the

(16) Melting points are uncorrected.

(17) M. M. Rauhut, I. Hechenbleikner, H. A. Currier, F. C. Schaefer and V. P. Wystrach, *THIS JOURNAL*, **81**, 1103 (1959).

(18) The spiran III is only moderately stable in aqueous solution in the absence of added acid while II is much more stable in this respect.

(19) This acetal liberates succinaldehyde readily under the conditions of the reaction.

mixture was kept at 0° for several hours. The mixture was then filtered and the solid washed with cold amyl alcohol, then an ether-acetone mixture and dried to give 23 g. (34%) of III, m.p. 84–86° dec. The only solvent from which this material was successfully recrystallized was 6:1 amyl alcohol-concentrated HCl, giving the analytical sample, m.p. 94–95° dec.

Anal. Calcd. for $C_8H_{18}ClO_2P$: C, 39.60; H, 6.65; Cl, 14.61; P, 12.77; mol. wt./2, 121.3. Found: C, 39.46; H, 6.55; Cl, 14.65; P, 12.85; mol. wt., 92.0 (cryoscopic in water¹⁵).

2,4,6-Triisopropyl-1,3-dioxo-5-phosphacyclohexane (VI) (Method A).—To 300 ml. of concentrated HCl was added 210 g. (2.9 moles) of isobutyraldehyde in the course of 2 hours while maintaining a temperature of 20–25°. To the resulting mixture was added 200 ml. of water and 200 ml. of petroleum ether (b.p. 30–60°) and the layers were separated. The aqueous phase was extracted with two further 200-ml. portions of petroleum ether and the extracts were combined and distilled. After removing the solvent there was obtained 169 g. (75%) of VI, b.p. 104–108° (11 mm.). Redistillation gave the analytical sample, b.p. 110° (14 mm.), n_D^{25} 1.4602.

Anal. Calcd. for $C_{12}H_{26}O_2P$: C, 62.04; H, 10.85; P, 13.34. Found: C, 61.82; H, 10.78; P, 13.26.

2,4,6-Triisopropyl-1,3-dioxo-5-phosphacyclohexane-5-inoic Acid (VIII).—A solution of 30.0 g. (0.13 mole) of VI in 200 ml. of 2-propanol was heated under reflux and blown with air for 40 hours. The solution was evaporated and the residue recrystallized from 2-propanol-water to give 20.1 g. (59%) of VIII, m.p. 155–156°. Further recrystallization raised the m.p. to 159–160°.

Anal. Calcd. for $C_{12}H_{26}O_4P$: C, 54.53; H, 9.53; P, 11.72; neut. equiv., 264.3. Found: C, 54.48; H, 9.59; P, 11.95; neut. equiv., 268.1.

Hydrolysis of VIII.—Eight grams (0.03 mole) of VIII, 10 ml. of concentrated HCl and 10 ml. of water were mixed in a distilling flask connected to a condenser and a receiver, which was immersed in a Dry Ice-bath. The apparatus was swept with a slow stream of nitrogen. The mixture was boiled gently and a homogeneous solution was obtained after 35 minutes; 5 ml. of additional distillate was then collected. The residual solution in the distilling flask was evaporated *in vacuo* to give 6.4 g. (100%) of bis-(1-hydroxy-2-methylpropyl)-phosphinic acid (IX), m.p. 163–165°. Recrystallization from acetonitrile containing a small amount of water gave the analytical sample, m.p. 168–169°.

Anal. Calcd. for $C_8H_{16}O_4P$: C, 45.71; H, 9.11; P, 14.74; neut. equiv., 210.2. Found: C, 45.78; H, 9.18; P, 14.73; neut. equiv., 209.8.

The distillate was dissolved in 150 ml. of ethanol and a solution of 6.0 g. (0.03 mole) of 2,4-dinitrophenylhydrazine, 30 ml. of concentrated H_2SO_4 , 150 ml. of ethanol and 35 ml. of water was added. After standing for 45 minutes the mixture was filtered giving 7.0 g. (92%) of the 2,4-dinitrophenylhydrazone of isobutyraldehyde, m.p. 169–174°. Recrystallization from ethanol-ethyl acetate gave a specimen with m.p. 179–180°, undepressed by an authentic sample.

5-(*p*-Chlorophenylcarbamoyl)-2,4,6-triisopropyl-1,3-dioxo-5-phosphacyclohexane (X).—A solution of 11.6 g. (0.05 mole) of VI, 7.7 g. (0.05 mole) of *p*-chlorophenyl isocyanate, 35 ml. of dry benzene and 4 drops of triethylamine was heated under reflux in a nitrogen atmosphere for 23 hr. The product crystallized upon cooling. It was collected, washed with cold benzene, and recrystallized from ethanol to give 8.6 g. (42%) of X, m.p. 158–160°. Further recrystallization gave material of m.p. 162–163°.

Anal. Calcd. for $C_{19}H_{29}ClNO_3P$: C, 59.14; H, 7.58; P, 8.03. Found: C, 58.88; H, 7.89; P, 8.14.

2,4,6-(3-Heptyl)-1,3-dioxo-5-phosphacyclohexane (VII) (Method A).—To a solution of 125 ml. of tetrahydrofuran and 125 ml. of concentrated HCl was added 79 g. (0.62 mole) of 2-ethylhexaldehyde in the course of 45 minutes while maintaining a temperature of 20–25°. Slow phosphine uptake continued for 1 hour; 75 ml. of petroleum ether was added and the layers were separated. The organic phase was distilled after removing solvent to give a 12.5-g. fraction of b.p. 50–70° (20 mm.), n_D^{25} 1.4202, which was shown to be unreacted 2-ethylhexanal. Further distillation gave 61.1 g. (75% conversion, 90% yield) of VII, b.p. 148–

153° (0.02 mm.). The analytical sample was a center cut, b.p. 149–150° (0.02 mm.), n_D^{25} 1.4709.

Anal. Calcd. for $C_{24}H_{46}O_2P$: C, 71.95; H, 12.33; P, 7.73. Found: C, 71.87; H, 12.35; P, 7.57.

Reaction of 2-Phenylpropionaldehyde and Phosphine (Method A).—This reaction was conducted as described for the preparation of VII using 134 g. of 2-phenylpropionaldehyde. The product was separated using benzene which was evaporated to give a colorless glass (142 g.). Treatment with hydrogen peroxide in acetic acid solution followed by dilution with water gave 17.7 g. of a white solid, m.p. 224–226°. Although the analytical data were in fairly good agreement with those calculated for tris-(1-hydroxy-2-phenylpropyl)-phosphine oxide, OH absorption was absent in the infrared in a Nujol mill.

Anal. Calcd. for $C_{27}H_{38}O_4P$: C, 71.66; H, 7.35; P, 6.85. Found: C, 71.55; H, 6.88; P, 6.94.

Bis-(2,2,2-trichloro-1-hydroxyethyl)-phosphine (XI) (Method B).—A solution of 49.6 g. (0.3 mole) of chloral hydrate in a mixture of 150 ml. of tetrahydrofuran and 50 ml. of concentrated HCl was prepared. Approximately 0.16 mole of phosphine was absorbed by this solution in 1.5 hours with a temperature rise from 25 to 45° being noted. The resulting solution was evaporated *in vacuo* and the residue was washed thoroughly with water and filtered to give 46.8 g. (95%) of XI, m.p. 125–127°. The analytical sample was prepared by recrystallization from benzene, m.p. 129–130° (previously reported⁶ 143°).

Anal. Calcd. for $C_4H_3Cl_3O_2P$: C, 14.61; H, 1.53; P, 9.42; mol. wt., 328.8. Found: C, 14.99; H, 1.69; P, 9.30; mol. wt., 331.0 (cryoscopic in ethylene carbonate).

Bis-(2,2,2-trichloro-1-hydroxyethyl)-phosphine Oxide (XII).—A solution of 2.0 g. (0.0061 mole) of XI in 20 ml. of acetic acid was treated with 2 ml. of 30% hydrogen peroxide. The solution became warm and solid precipitated. After 1 hour the mixture was filtered and the solid washed with ether to give 1.6 g. (76%) of XII as a white powder, m.p. 195° dec. The melting point of the analytical sample (from glacial acetic acid) was unchanged.

Anal. Calcd. for $C_4H_3Cl_3O_3P$: C, 13.93; H, 1.46; P, 8.98. Found: C, 14.43; H, 1.68; P, 8.83.

Reaction of XI with Phenyl Isocyanate.—A mixture of 3.3 g. (0.01 mole) of XI, 4.8 g. (0.04 mole) of phenyl isocyanate, 20 ml. of benzene and 3 drops of triethylamine was heated under reflux for 4 hours. The benzene was evaporated and the residual material washed with petroleum ether and recrystallized from ethyl acetate, then acetic acid to give 1.15 g. (29%) of tris-(phenylcarbamoyl)-phosphine (XIII), m.p. 212–213°, identical with an authentic specimen.¹⁶

Bis-(2,2-dichloro-1-hydroxyethyl)-phosphine (XIV) (Method B).—A solution of 35.4 g. (0.32 mole) of dichloroacetaldehyde, 75 ml. of concentrated HCl, and 75 ml. of tetrahydrofuran was treated with phosphine on the Parr apparatus. A total of 0.17 mole of phosphine was taken up in 4 hours. The resulting solution was neutralized with aqueous sodium hydroxide and extracted several times with ether. The extracts were dried over sodium sulfate and evaporated to give 18.2 g. of XIV as a colorless liquid. A portion was oxidized with hydrogen peroxide in refluxing methanol. After evaporation of the solvent, the residue was washed with ether and collected to give bis-(2,2-dichloro-1-hydroxyethyl)-phosphinic acid (XV), m.p. 195° dec. after recrystallization from acetonitrile.

Anal. Calcd. for $C_4H_7Cl_2O_2P$: Cl, 48.59; P, 10.61. Found: Cl, 48.85; P, 10.31.

The aniline salt of XV was prepared by treatment with excess aniline in methanol; m.p. 175° dec. after recrystallization from 2-propanol.

Anal. Calcd. for $C_{10}H_{14}Cl_2NO_4P$: Cl, 36.84; N, 3.64; P, 8.05. Found: Cl, 37.00; N, 3.38; P, 7.77.

Preparation of XV from Hypophosphorous Acid and Dichloroacetaldehyde.—A solution of 67 g. (0.6 mole) of dichloroacetaldehyde, 33 g. (0.25 mole) of 50% aqueous hypophosphorous acid and 100 ml. of methanol was heated under reflux for 18 hours. The solution was then evaporated *in vacuo* and the residue triturated with ether and filtered to give 15 g. (21%) of XV, m.p. 185–192°. Recrystallization from acetonitrile gave a sample with m.p.

194° dec. whose infrared spectrum was identical with that of the sample obtained by oxidizing XIV.

Reaction of Heptanal and Phosphine in the Presence of a Small Amount of HCl (Method B).—A solution of 24.6 g. (0.216 mole) of heptanal, 185 ml. of tetrahydrofuran and 2.08 g. (0.0216 mole) of 38.0% by weight HCl was treated with excess phosphine for 1 hour. The precipitated solid was collected giving 10.5 g. of tetrakis-(1-hydroxyheptyl)-phosphonium chloride, m.p. 123–124°. An additional 0.8 g., m.p. 122–123°, was recovered from the filtrate (total yield 99% based on HCl) along with 10.4 g. of unreacted heptanal, b.p. 40–42° (10 mm.).

Reaction of Phosphine and Heptanal in the Presence of Aluminum Chloride (Method B).—To a suspension of 13.3 g. (0.1 mole) of aluminum chloride in 150 ml. of dry chloroform was added 11.4 g. (0.1 mole) of heptanal with cooling to give a pale orange solution. Uptake of phosphine was vigorous and complete in 20 minutes. The solution was then hydrolyzed cautiously under nitrogen with 100 ml. of 2 *N* HCl. The chloroform layer was washed with 2 *N* HCl and water, separated, dried with sodium sulfate, and evaporated to give 13 g. of a colorless, pyrophoric liquid which had a foul odor. The infrared spectrum showed strong peaks at 3350 and 2290 cm^{-1} . Approximately

80% of this liquid distilled over a wide range at low pressures, but no plateau was observed. Heptanal was present in the distillate, although none was detected in the original liquid.

Reaction of Phosphine and Heptanal in the Presence of Aluminum Chloride (Method A).—A suspension of 35 g. (0.26 mole) of aluminum chloride in 400 ml. of dry chloroform was prepared and dry phosphine passed in until no more was absorbed. While maintaining a slow stream of phosphine, 30 g. (0.26 mole) of heptanal was added with external cooling to maintain a temperature of 20–25°. The mixture was hydrolyzed with 400 ml. of 3 *N* HCl and the chloroform layer was separated, washed with water, and dried with sodium sulfate. A yellow suspension was removed by filtration with the aid of Hyflo. The chloroform was evaporated to give a pyrophoric liquid which partially crystallized on exposure to air overnight. This was triturated with ether and filtered to give 12.4 g. (35%) of tris-(1-hydroxyheptyl)-phosphine oxide, m.p. 112–115°. Repeated recrystallization from ethyl acetate, then cyclohexane, gave the analytical sample, m.p. 113–114°. The infrared spectrum showed strong OH and P→O bands at 3150 and 1135 cm^{-1} , respectively.

Anal. Calcd. for $\text{C}_{21}\text{H}_{45}\text{O}_4\text{P}$: C, 64.25; H, 11.56. Found: C, 63.94; H, 11.76.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF STATE UNIVERSITY OF NEW YORK, LONG ISLAND CENTER, OYSTER BAY, N. Y.]

New Reactions of Phosphite Esters: The Conversion of Phthalic Anhydride into Biphthalyl by Trialkyl Phosphites and into Phthalide-3-phosphonates by Dialkyl Phosphites¹

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Triethyl phosphite effects the conversion of phthalic anhydride into biphthalyl (III) in 70% yield. This new reaction is a convenient route to enediol-dilactones and hence to substituted benzoin. The conversion of tetrachlorophthalic anhydride into octachlorobiphthalyl (XIV) by triethyl phosphite is very rapid: $2\text{O}=\text{COC}=\text{O} + 2(\text{C}_2\text{H}_5\text{O})_3\text{P} \rightarrow \text{O}=\text{COC}=\text{COC}=\text{O} + 2(\text{C}_2\text{H}_5\text{O})_3\text{PO}$.

If phthalic anhydride (1 mole) is allowed to react with a trialkyl phosphite, $(\text{RO})_3\text{P}$ (excess), in the presence of a dialkyl phosphite, $(\text{R}'\text{O})_2\text{P}(\text{O})\text{H}$ (1 mole), practically no biphthalyl is formed; instead, a phthalide-3-phosphonate, $\text{O}=\text{COCHP}(\text{O})(\text{OR}')_2$, is produced in excellent yield. The same phthalidephosphonate can be made from *o*-phthalaldehydic acid and the dialkyl phosphite. It is suggested that the phosphorus atom of a phosphite ester attacks the oxygen of the anhydride carbonyl; the resulting intermediate generates a carbene and a *phosphate ester*. The carbene can either dimerize to biphthalyl or can be trapped by reaction with a dialkyl phosphite.

We have investigated the reaction of trialkyl phosphites with *p*-quinones,² *o*-quinones³ and α -diketones.³ Prompted by the formal analogy between quinones and cyclic unsaturated anhydrides we undertook an investigation of the reaction of trialkyl phosphites with phthalic anhydride and with substituted phthalic anhydrides. The results are reported in this paper.

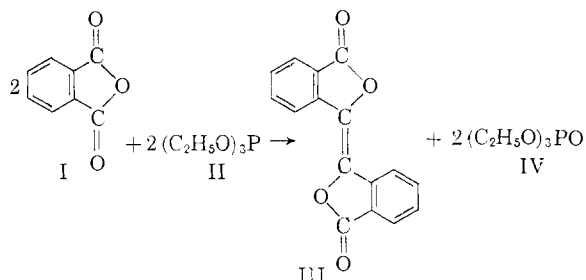
Results

It was found that triethyl phosphite (II) effected the conversion of phthalic anhydride (I) into biphthalyl (III) in satisfactory yield (70%). The reaction was carried out in an excess of the phosphite as solvent and the biphthalyl separated from the solution in nearly pure state. Table I summarizes the results of a typical experiment.

(1) This work is being supported by the National Science Foundation (Grant NSF G 9917). Preliminary experiments were carried out (O.H.B.) at Columbia University under grants from the Public Health Service (Grants CY-3250 and RG-6136 A). Preliminary communication: F. Ramirez, H. Yamanaka and O. H. Basedow, *J. Org. Chem.*, **24**, 1838 (1959).

(2) (a) F. Ramirez, E. H. Chen and S. Dershowitz, *THIS JOURNAL*, **81**, 4338 (1959); (b) F. Ramirez and S. Dershowitz, *ibid.*, **81**, 587 (1959).

(3) F. Ramirez and N. B. Desai, *ibid.*, **82**, 2652 (1960).



It can be seen that most of the excess triethyl phosphite was isomerized to diethyl ethylphosphonate, $\text{C}_2\text{H}_5\text{P}(\text{O})(\text{OC}_2\text{H}_5)_2$, during the reaction. Pure triethyl phosphite was not changed under comparable conditions. The stoichiometric amount of triethyl phosphite (IV) was produced only when air was carefully excluded. Otherwise, a great deal of the excess triethyl phosphite was converted into triethyl phosphate, as can be seen from Table II. Molecular oxygen had no effect on pure triethyl phosphite under comparable conditions.

The reaction of other trialkyl phosphites with phthalic anhydride was examined and the results are given in Table III. Trimethyl phosphite was