well extending about half-way into the packed section of the tube.[18] The temperature was controlled to ±6°.

The optimum rate of addition of phosphate during pyrolysis appeared to be about 0.3 g. of ester per minute, although little change in the yield of olefin occurred when the rate was varied from 0.06 to 0.3 g. per minute. The crude pyrolysate was purified by distillation through an 8-in. Vigreux column. The olefin fraction boiling in the range of temperatures given in the literature[19] for the expected olefin and isomerization products was collected for infrared analysis.[20] No attempt was made to identify other byproducts. After a run the tube was usually clean throughout except for an approximately 2-in. area about 1 in. from the top of the packing, which was black. Etching of the tube in this area took place.

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[18] A number of tube designs, including all-glass construction, have been employed to permit insertion of the thermocouple well and the dropping funnel into the relatively small tube opening. The simplest of these (and the easiest to disassemble and clean) was a tube terminating in an open cup of about 35-mm. o.d. The dropping funnel and thermocouple well were fitted into the cup with a clean rubber stopper. This device was very satisfactory provided that in inserting the pyrolysis tube into the apparatus it was first fitted with a 1.25-in. sleeve of 1-in. copper tubing and a fairly tight-fitting shield formed from a 2-in. square of asbestos cement board (Transite) (to conduct away the heat and to seal off the opening of the furnace, respectively). Otherwise, the rubber stopper charred badly at the higher temperatures.

[19] S. W. Ferris, "Handbook of Hydrocarbons," Academic Press, Inc., New York, N. Y., 1955.

[20] Infrared determinations were made by Mr. E. R. Magnuson with a Perkin-Elmer recording instrument, model 21, employing sodium chloride optics and the neat liquid or gas.

LINCOLN 8, NEBRASKA

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

Phosphonic Acids. IV.[1] Preparation and Reactions of β-Ketophosphonate and Enol Phosphate Esters[2]

BY HERBERT I. JACOBSON, MARTIN J. GRIFFIN, SEYMOUR PREIS AND ELWOOD V. JENSEN

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In contrast to α-chlorinated ketones which react with triethyl phosphite to form enol phosphate esters, α-iodoketones react "normally" with triethyl phosphite to yield β-ketophosphonate esters. Thus iodoacetone reacts with triethyl phosphite at room temperature to form diethyl β-ketopropylphosphonate (II). Diethyl β-ketopropylphosphonate also may be prepared by the acid-catalyzed ethanolysis of diethyl 3-diethylphosphonoisopropenyl phosphate (IIIb), a substance which is obtained by the smooth reaction of two moles of triethyl phosphite with α,α′-dichloroacetone. Treatment of diethyl 3-diethylphosphonoisopropenyl phosphate (IIIb) with sodium ethoxide in boiling ethanol results in the elimination of the elements of diethyl hydrogen phosphate to form diethyl propynylphosphonate (VI). Hydrogenation of diethyl isopropenyl phosphate (VIII) over palladium yields diethyl isopropyl phosphate (IX), whereas over platinum reductive cleavage of the enol ester linkage takes place to form diethyl hydrogen phosphate (X).

It has long been recognized that the reaction of α-chloroketones with sodium diethyl phosphonate[3] and with triethyl phosphite[4] gives rise to unusual products which, although originally formulated as β-ketophosphonates, do not react with the usual carbonyl reagents and which, on acid hydrolysis, undergo cleavage to produce a ketone and inorganic phosphate. The reason for this behavior became clear when it was demonstrated that the reaction of triethyl phosphite with α-chlorinated aldehydes[5] and ketones[6,7] takes place in a manner different from that of simple alkyl halides to yield predominantly enol phosphate esters rather than β-ketophosphonate esters. The most reasonable explanation proposed for this phenomenon is that the polarization induced by the electronegative halogen atoms causes the attack of triethyl phosphite to take place not on the carbon atom bearing the halogen but rather on the carbon atom of the carbonyl group with subsequent concerted rearrangement.[8]

In connection with the synthesis of phosphonate analogs of certain phosphorylated intermediates of metabolism,[1] a method was desired for the preparation of authentic β-ketophosphonate esters. If it is assumed that chloro and polyhaloketones react abnormally in the Arbuzov reaction because of the polarization induced on the carbonyl group by the electronegative halogen atoms, it was considered that an iodoketone might react normally since the less electronegative iodine atom would exert a smaller polarization effect as well as being more reactive toward simple displacement. Accordingly, the reaction of iodoacetone (I) with triethyl phosphite was investigated and found to proceed exothermically at room temperature to produce diethyl β-ketopropylphosphonate (II), with only a small amount of diethyl isopropenyl phosphate being formed.[9] This β-ketophosphonate (II) forms the expected 2,4-dinitrophenylhydrazone derivative, and its infrared spectrum shows strong carbonyl absorption at 1717 cm.$^{-1}$ and

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[1] Paper III, S. Preis, T. C. Myers and E. V. Jensen, THIS JOURNAL, **77**, 6225 (1955).

[2] This investigation was supported in part by a grant from the National Institutes of Health, Public Health Service (RG-3053).

[3] P. Nylen, Dissertation, Uppsala, 1930, p. 59; I. S. Bengelsdorf, Ph.D. Dissertation, University of Chicago, 1951, p. 18.

[4] B. A. Arbuzov, B. P. Lugovkin and N. P. Bogonostseva, *Zhur. Obshchei Khim.*, **20**, 1468 (1950); *C. A.*, **45**, 1506 (1951).

[5] (a) W. Perkow, *Ber.*, **87**, 755 (1954); (b) W. Perkow, E. W. Krockow and K. Knoevenagel, *ibid.*, **88**, 662 (1955).

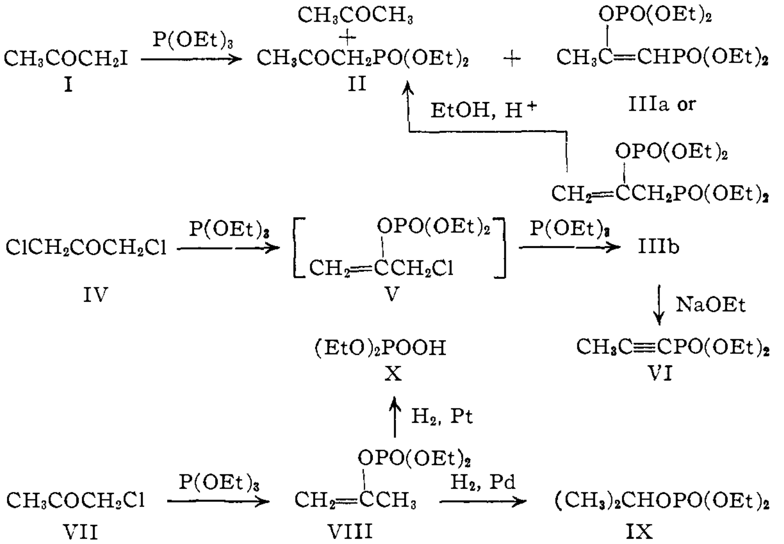
[6] (a) J. F. Allen and O. H. Johnson, THIS JOURNAL, **77**, 2871 (1955); (b) J. F. Allen, S. K. Reed, O. H. Johnson and N. J. Brunsvold *ibid.*, **78**, 3715 (1956).

[7] (a) A. N. Pudovik and N. M. Lebedeva, *Doklady Akad. Nauk S.S.S.R.*, **101**, 889 (1955); *C. A.*, **50**, 3219 (1956); (b) A. N. Pudovik, *Zhur. Obshchei Khim.*, **25**, 2173 (1955); *C. A.*, **50**, 8486 (1956); (c) A. N. Pudovik, *Doklady Akad. Nauk S.S.S.R.*, **105**, 735 (1955); *C. A.*, **50**, 11230 (1956).

[8] M. S. Kharasch and I. S. Bengelsdorf, *J. Org. Chem.*, **20**, 1356 (1955).

[9] Since the completion of this work, Pudovik[7b,c] has reported the reaction of iodoacetone with triethyl phosphite in boiling diethyl ether to produce diethyl β-ketopropylphosphonate (II) accompanied by small amounts of diethyl isopropenyl phosphate. No mention is made of the formation of the higher boiling phosphate-phosphonate ester III.

P=O absorption near the normal phosphonate region at 1258 cm.$^{-1}$.



From the reaction of iodoacetone with triethyl phosphite, there was also isolated, besides ethyl iodide and a small amount of diethyl ethylphosphonate, significant amounts of acetone and of a higher boiling material which was shown to be a diethyl diethylphosphonoisopropenyl phosphate[10] (III). As described below, the latter substance can be transformed into diethyl β-ketopropylphosphonate by ethanolysis of the enol phosphate linkage.

The mechanism of the formation of acetone and the phosphate-phosphonate III presents an interesting problem. Inasmuch as the presence of a small amount of hydrogen iodide was noted during the distillation of the reaction product, it was considered that this material may act catalytically to reduce iodoacetone to acetone liberating iodine which then reacts either with iodoacetone or with the activated methylene group of the β-ketophosphonate II to regenerate hydrogen iodide and form either α,α′-diiodoacetone or diethyl α-iodo-β-ketopropylphosphonate. Either of these substances conceivably could react with triethyl phosphite to form III. However, in an experiment designed to eliminate the presence of hydrogen iodide by carrying out all steps under anaerobic conditions in the dark in the presence of solid potassium carbonate, substantial amounts of III again were produced, although in this case no hydrogen iodide was detectable. Therefore, the mechanism of the formation of the phosphate-phosphonate III remains uncertain.

Since an enol phosphate ester linkage represents a potential carbonyl group, an alternative route to diethyl β-ketopropylphosphonate was suggested. It has been reported[6a] that α,α′-dichloroacetone reacts with one mole of triethyl phosphite to form diethyl 3-chloroisopropenyl phosphate, a substance which still contains one chlorine atom which now should be capable of replacement by a phosphonate group in the normal Arbuzov reaction. Accordingly, the reaction of α,α′-dichloroacetone with excess triethyl phosphite was investigated and found to proceed smoothly with the evolution of two moles of ethyl chloride to produce diethyl 3-diethylphosphonoisopropenyl phosphate (IIIb).[11] In contrast to its reaction with chloroacetone which requires a temperature of at least 150°, it is noteworthy that the reaction of the first mole of triethyl phosphite with α,α′-dichloroacetone took place at room temperature.

On prolonged heating with absolute ethanol in the presence of a catalytic amount of *p*-toluenesulfonic acid, ethanolysis of the enol phosphate linkage of IIIb took place affording a 63% yield of diethyl β-ketopropylphosphonate (II) accompanied by triethyl phosphate.

When an ethanolic solution of the phosphate-phosphonate IIIb was treated with one mole of sodium ethoxide at room temperature, the enol phosphate linkage was destroyed rapidly as indicated by the disappearance of the characteristic enol absorption band at 1640 cm.$^{-1}$. However, this base-induced cleavage gave not only triethyl phosphate and diethyl β-ketopropylphosphonate, but also substantial amounts of diethyl propynylphosphonate (VI) and, after acidification, diethyl hydrogen phosphate. When the reaction of IIIb with sodium ethoxide was carried out at elevated temperature, the elimination of the elements of diethyl hydrogen phosphate took place to the exclusion of the ethanolysis reaction affording diethyl propynylphosphonate (VI) in 69% yield.

The product from the reaction of sodium ethoxide with IIIb is assigned the structure of diethyl propynylphosphonate (VI) rather than the isomeric diethyl propargylphosphonate on the basis of its infrared spectrum (triple bond stretching at 2210 cm.$^{-1}$ typical of disubstituted acetylenes rather than 2100–2140 as in monosubstituted acetylenes as well as the absence of the characteristic ≡CH stretching absorption at 3300 cm.$^{-1}$) and the fact that it does not react with ammoniacal silver nitrate. The formation of VI from IIIb may involve the allene, $H_2C{=}C{=}CHPO(OEt)_2$, as an intermediate; investigations of this possibility are in progress and will be reported separately. An attempt was made to prepare authentic diethyl propargylphosphonate for comparison by the reaction of triethyl phosphite with propargyl bromide. This reaction did not proceed in a straightforward manner, but yielded chiefly a mixture of high boiling unstable products accompanied by a very small amount of a material apparently identical with VI.

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[10] Inasmuch as there were minor differences between the infrared spectrum of this substance and that of the product obtained from dichloroacetone which undoubtedly possesses the structure IIIb, it is not yet certain whether structure IIIa or IIIb is the correct one in this case.

[11] Since the completion of this work, a similar preparation of diethyl 3-diethylphosphonoisopropenyl phosphate from dichloroacetone has been reported.[7c]

In confirmation of the observations of others,[6a,7] the reaction of chloroacetone (VII) with triethyl phosphite was found to produce predominantly diethyl isopropenyl phosphate (VIII) accompanied by small amounts of diethyl β-ketopropylphosphonate. The structure of VIII was confirmed by its unique infrared spectrum (enol band at 1646 cm.$^{-1}$ and phosphate-type P=O stretching band at 1270 cm.$^{-1}$ rather than phosphonate-type at 1240–1250 cm.$^{-1}$), by ozonolysis to produce formaldehyde and by hydrogenation over palladium to produce diethyl isopropyl phosphate (IX) identical with an authentic sample of the latter substance prepared by the method of Atherton and Todd.[12]

When the hydrogenation of diethyl isopropenyl phosphate was carried out using a platinum catalyst, two moles of hydrogen per mole of compound were absorbed to produce diethyl hydrogen phosphate (X) and presumably propane, although the latter substance was not isolated. Thus, the reductive cleavage of an enol phosphate bond under these conditions is similar to the cleavage which is known to take place when enol esters of carboxylic acids are hydrogenated with a platinum catalyst.[13]

An attempt was made to prepare diethyl β-ketopropylphosphonate from chloroacetone by blocking the carbonyl group as the ethylene ketal. It was found that the dioxolane of chloroacetone, prepared according to Kühn,[14] did not react with triethyl phosphite at 160° nor with sodium diethylphosphonate in boiling tetrahydrofuran.

Experimental[15]

Diethyl β-Ketopropylphosphonate (II) **from Iodoacetone** (I).—Freshly distilled iodoacetone (52.2 g., 0.28 mole), b.p. 68–69° (24 mm.), prepared by the reaction of potassium iodide with chloroacetone in aqueous ethanol,[16] was added[17] slowly with stirring to triethyl phosphite (47.3 g., 0.29 mole) held at 0–5°. After the addition was complete, the cold bath was removed, whereupon the reaction mixture warmed spontaneously to about 35° and remained at this temperature for 2 hr. when the temperature began to fall. Distillation of the reaction mixture at reduced pressure yielded, in addition to a forerun (13.6 g.) and a high boiling residue (15.0 g.), diethyl β-ketopropylphosphonate (II), 15.5 g., 30%, b.p. 83–84° (0.4 mm.), n^{25}D 1.4310, reported[7b] b.p. 126° (9 mm.), n^{20}D 1.4350, with characteristic infrared absorption peaks at 1165, 1258 and 1717 cm.$^{-1}$.

Anal. Calcd. for $C_7H_{15}O_4P$: C, 43.30; H, 7.79; P, 15.99. Found: C, 43.00; H, 7.94; P, 16.12.

Treatment of this product with 2,4-dinitrophenylhydrazine in methanol–sulfuric acid solution gave the 2,4-dinitrophenylhydrazone derivative, m.p. 104.9–105.5°.

Anal. Calcd. for $C_{13}H_{19}O_7N_4P$: N, 14.96. Found: N, 15.11.

Redistillation of the 13.6 g. of forerun yielded crude diethyl isopropenyl phosphate, 7.2 g., 14%, b.p. 60–68° (1.5 mm.), n^{25}D 1.4136, plus an additional amount of diethyl β-ketopropylphosphonate, 6.2 g., 12%, bringing the total yield of the latter material to 42%. The residue from the original distillation (15.0 g.) was molecularly distilled to yield diethyl diethylphosphonoisopropenyl phosphate (III), 14.0 g., 0.04 mole, n^{25}D 1.4469, with characteristic infrared absorption peaks[18] at 1149, 1252, 1290 and 1650 cm.$^{-1}$.

Anal. Calcd. for $C_{11}H_{24}O_7P_2$: C, 40.00; H, 7.32; P, 18.77. Found: C, 39.93; H, 7.41; P, 18.50.

When this product was heated in absolute ethanol in the presence of *p*-toluenesulfonic acid, infrared analyses of test portions showed a progressive decrease in the intensity of the enol absorption (1648 cm.$^{-1}$) with the appearance and increase of carbonyl absorption (1717 cm.$^{-1}$).

In a similar experiment, triethyl phosphite (74 g., 0.45 mole) and iodoacetone (77 g., 0.42 mole) gave 29.2 g., 38%, of crude diethyl β-ketopropylphosphonate (II), n^{25}D 1.4300, which on redistillation gave 21.9 g., 28%, of purified product, n^{25}D 1.4340. Redistillation of the forerun (7.1 g.) yielded 3.7 g., 5%, of diethyl isopropenyl phosphate plus an additional 2.0 g., 3%, of diethyl β-ketopropylphosphonate. Distillation of the high boiling residue (32.5 g.) through a small Claisen flask gave diethyl diethylphosphonoisopropenyl phosphate, 30 g., 0.09 mole, boiling from 125° (0.10 mm.) to 136° (0.14 mm.), n^{25}D 1.4465.

During the distillation of the original reaction mixture, 86.5 g. of volatile material collected in the −80° trap, and one gram of a fuming substance which appeared to be hydrogen iodide collected in a subsequent trap cooled in liquid nitrogen. Redistillation of the volatile product through a Fenske column yielded acetone, 6.4 g., 0.11 mole, b.p. 55–56°, n^{25}D 1.3850, m.p. of dinitrophenylhydrazone derivative, 123.5–124.5°; ethyl iodide, 40.7 g., 0.26 mole, b.p. 71–72°, n^{25}D 1.5074; and a third product which appeared to be diethyl ethylphosphonate, 5.2 g., 0.03 mole, b.p. 78–88° (16 mm.), n^{25}D 1.4120.

In an attempt to prevent the formation of the high boiling product (III) by eliminating the presence of hydrogen iodide in the reaction system, iodoacetone (26.5 g., 0.14 mole), freshly distilled in subdued light into a receiver containing a small amount of solid potassium carbonate, and triethyl phosphite (22.8 g., 0.14 mole) were allowed to react in the dark in an atmosphere of nitrogen in the presence of a little potassium carbonate. As before, the mixture warmed spontaneously to 35° for about 2 hr. On distillation of the reaction mixture in subdued light, no trace of hydrogen iodide was noticeable in the liquid nitrogen-cooled trap, but the yield of diethyl β-ketopropylphosphonate, 7.8 g., 33%, was approximately the same as in previous experiments, and 7.0 g., 0.021 mole, of the high boiling product (III) was obtained.

Diethyl 3-Diethylphosphonoisopropenyl Phosphate (**IIIb**) **from** α,α′-**Dichloroacetone.**—To recrystallized α,α′-dichloroacetone (10.0 g., 0.079 mole) one molar equivalent of triethyl phosphite (13.1 g., 0.079 mole) was added at such a rate that the temperature of the stirred reaction mixture which warmed spontaneously, and evolved ethyl chloride was maintained at about 50°. When the addition was complete and the temperature began to drop, an additional equivalent of triethyl phosphite (13.1 g., 0.079 mole) was added in one portion and the reaction mixture heated at 160° for 2 hr. After the evolution of ethyl chloride (8.3 g., 82%) had ceased, the mixture was cooled, and the small amount of unreacted triethyl phosphite was removed at reduced pressure. The residue (14 g.) was molecularly distilled to yield diethyl 3-diethylphosphonoisopropenyl phosphate (IIIb), 12.9 g., 50%, n^{25}D 1.4429, reported[7c] n^{20}D 1.4435, with characteristic infrared absorption peaks at 1164, 1272 and 1650 cm.$^{-1}$.

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(12) F. R. Atherton and A. R. Todd, *J. Chem. Soc.*, 674 (1947).

(13) H. H. Inhoffen, G. Stoeck, C. Kölling and V. Stoeck, *Ann.*, **568**, 52 (1950).

(14) M. Kühn, *J. prakt. Chem.*, [2] **156**, 103 (1940).

(15) Microanalyses were carried out by Mr. William Saschek, by Micro-Tech Laboratories, Skokie, Ill., and by the Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Infrared spectra were determined as liquid films unless otherwise specified. The authors are grateful to Dr. Marcel Harnik for carrying out many of the infrared determinations involved in this study.

(16) R. Scholl and G. Mattaiopoulos, *Ber.*, **29**, 1550 (1896).

(17) If the triethyl phosphite is added to excess iodoacetone, the reaction mixture turns dark.

(18) The infrared spectrum of this substance was identical with that of diethyl diethylphosphonoisopropenyl phosphate (IIIb) obtained from the reaction of triethyl phosphite with α,α′-dichloroacetone except for a slight modification and broadening of the P=O bands at 1252 and 1290 cm.$^{-1}$ and the presence of an additional moderately strong band at 1149 cm.$^{-1}$ which obscures partially the POEt band at 1165 cm.$^{-1}$.

Anal. Calcd. for $C_{11}H_{24}O_7P_2$: C, 40.00; H, 7.32; P, 18.77; neut. equiv., 165. Found: C, 39.73; H, 7.27; P, 18.20; neut. equiv., 169.[19]

A subsequent experiment was carried out in a similar fashion except that a 50% excess of triethyl phosphite was employed. Thus, from α,α'-dichloroacetone (97 g., 0.76 mole) and triethyl phosphite (378 g., 2.28 moles) there was obtained a crude product (238 g., 95%, n^{25}_{D} 1.4432) which on distillation in a Claisen flask yielded purified diethyl 3-diethylphosphonoisopropenyl phosphate (IIIb), 210 g., 84%, b.p. 118–120° (0.05 mm.), n^{25}_{D} 1.4459, with an infrared spectrum identical with that of the analyzed sample of this substance.

Diethyl β-Ketopropylphosphonate (II) from IIIb.—A solution of diethyl 3-diethylphosphonoisopropenyl phosphate (IIIb, 25.4 g., 0.077 mole) and *p*-toluenesulfonic acid (250 mg.) in 100 ml. of absolute ethanol was heated under reflux for 24 days until infrared analysis of test portions showed complete disappearance of enol absorption and no further increase in the carbonyl absorption. The reaction mixture was deacidified by passage through a column containing 100 g. of Amberlite IRA-410 (OH) resin which had been washed thoroughly with ethanol. The eluate was stirred with 2.0 g. of barium hydroxide whereupon 4.8 g. of a solid precipitate slowly formed and was removed by filtration. Recrystallization of this solid from 80% alcohol gave barium diethyl phosphate derived from the triethyl phosphate produced in the ethanolysis reaction.

Anal. Calcd. for $C_8H_{20}P_2Ba$: C, 21.66; H, 4.54; P, 13.97. Found: C, 21.69; H, 4.73; P, 14.31.

The alcohol was evaporated from the above filtrate, and the residue (16.8 g.) was distilled at reduced pressure to yield, after a small forerun, diethyl β-ketopropylphosphonate (II), 9.4 g., 63%, b.p. 80–89° (1.0 mm.), n^{25}_{D} 1.4300, with an infrared spectrum identical with that of the analyzed sample of this material prepared from iodoacetone. The 2,4-dinitrophenylhydrazone of this product melted at 105.0–105.7°, not depressed by admixture with the derivative of the authentic diethyl β-ketophosphonate, m.p. 104.9–105.2°.

Reaction of IIIb with Sodium Ethoxide at Room Temperature.—A solution of crude diethyl 3-diethylphosphonoisopropenyl phosphate (IIIb, 66 g., 0.20 mole) in 80 ml. of absolute ethanol was added to 200 ml. of absolute ethanol in which metallic sodium (4.6 g., 0.20 mole) had been dissolved. After standing 1 hr. at room temperature, infrared analysis of a neutralized test portion indicated complete disappearance of enol absorption (1640 cm.$^{-1}$) with the appearance of strong carbonyl absorption (1717 cm.$^{-1}$), was well as a sharp, fairly strong peak at 2222 cm.$^{-1}$ typical of acetylenic compounds. After 2 hr., the reaction mixture was freed of alkali by passage through a column of Amberlite IR-120 resin which had been washed with ethanol. The alcohol was evaporated from the eluate at reduced pressure, and the residual oil was distilled through a small Vigreux column to yield triethyl phosphate, 16.7 g., b.p. 56.5–59° (0.5 mm.), n^{25}_{D} 1.4060, reported[20] n^{25}_{D} 1.4039.

Anal. Calcd. for $C_6H_{15}O_4P$: C, 39.62; H, 8.24; P, 17.00. Found: C, 39.62; H, 8.09; P, 16.86.

This was followed by a series of fractions (total wt. 24.9 g.) boiling from 63 to 86° (0.5 mm.), n^{25}_{D} 1.4200 to 1.4350, which, from their infrared spectra, appeared to be mixtures of diethyl alkylphosphonates possessing both carbonyl and alkyne absorption. There remained a high boiling, acidic residue, 16.1 g., the infrared spectrum of which was practically identical with that of the analyzed sample of diethyl hydrogen phosphate (X) described below.

Fractionation of a portion of the combined mixture of the phosphonate esters through a Podbielniak Heliband column yielded a small amount of diethyl β-ketopropylphosphonate (II), b.p. 65° (0.8 mm.), n^{25}_{D} 1.4307, several larger fractions showing progressively less carbonyl and more alkyne absorption and, finally, a small fraction of apparently pure diethyl propynylphosphonate (VI), b.p. 73° (0.8 mm.), n^{25}_{D} 1.4432.

Anal. Calcd. for $C_7H_{13}O_3P$: C, 47.73; H, 7.44. Found: C, 47.34; H, 7.56.

Diethyl Propynylphosphonate (VI) from IIIb.—Diethyl 3-diethylphosphonoisopropenyl phosphate (IIIb, 33 g., 0.10 mole) was added over a 0.5-hr. period to a refluxing solution of sodium (2.28 g., 0.099 mole) in 70 ml. of absolute ethanol with stirring in an atmosphere of dry nitrogen. The cooled orange-colored reaction mixture was then both neutralized and freed of diethyl hydrogen phosphate by passage through a column of 750 ml. of Amberlite MB-1 resin which had been previously washed with 750 ml. of 95% ethanol followed by 300 ml. of absolute ethanol. The ethanol was evaporated from the eluate and the residue (21.6 g.) distilled at reduced pressure. After a 6-g. forerun, there was obtained diethyl propynylphosphonate (VI), 12.0 g., 69%, b.p. 108–110° (2.1 mm.), n^{25}_{D} 1.4449, with characteristic infrared absorption peaks at 1168, 1270 and 2210 cm.$^{-1}$.

Anal. Calcd. for $C_7H_{13}O_3P$: C, 47.73; H, 7.44; P, 17.59. Found: C, 47.73; H, 7.59; P, 17.36.

Reaction of Triethyl Phosphite with Propargyl Bromide.—A mixture of propargyl bromide (31.7 g., 0.266 mole) and triethyl phosphite (43.2 g., 0.26 mole) was heated to 90° whereupon a vigorous exothermic reaction took place. After this reaction had subsided (30 minutes) the mixture was heated under reflux for 1 hr. An additional amount of triethyl phosphite (21.6 g., 0.13 mole) was added and heating continued for another hour. Ethyl bromide (17.9 g., 0.16 mole) was collected in a cold trap. Distillation of the red-brown residue under reduced pressure yielded, after a forerun of triethyl phosphite, a substance apparently identical in its properties and infrared spectrum with diethyl propynylphosphonate (VI), 2.3 g., 5%, b.p. 98–103° (2 mm.), n^{25}_{D} 1.4453.

Anal. Calcd. for $C_3H_{13}O_3P$: C, 47.73; H, 7.44; P, 17.59. Found: C, 47.65; H, 7.59; P, 17.33.

The major distillable product (13 g.) was a higher boiling material, b.p. 150–152° (0.2 mm.), n^{25}_{D} 1.4756, which was unstable on storage. The structure of this material has not as yet been determined.

Anal. Found: C, 45.24; H, 7.61; P, 16.45.

A non-volatile residue (27 g.) remained in the still-pot.

Diethyl Isopropenyl Phosphate (VIII).—A mixture of redistilled chloroacetone (25 g., 0.27 mole) and triethyl phosphite (50 g., 0.30 mole) was heated for 4 hr. at 165°. During this time ethyl chloride (17.1 g., 0.26 mole) and 1 g. of higher boiling material were evolved and collected in a cold trap. The reaction mixture was cooled and distilled at reduced pressure. Crude diethyl isopropenyl phosphate (45 g.) was collected at 56–65° (0.1 mm.). A portion of this product was redistilled through a Podbielniak Heliband micro-column to yield pure VIII, b.p. 57° (0.6 mm.), n^{25}_{D} 1.4158; reported b.p. 72–73° (1 mm.),[6a] 96° (12 mm.),[7b] n^{35}_{D} 1.4135,[6a] n^{20}_{D} 1.4190,[7b] with characteristic infrared absorption peaks at 1165, 1270 and 1646 cm.$^{-1}$.

Anal. Calcd. for $C_7H_{15}O_4P$: C, 43.30; H, 7.79; P, 15.96. Found: C, 42.55; H, 7.93; P, 16.13.

In a similar experiment, the reaction product of chloroacetone (50 g., 0.54 mole) and triethyl phosphite (100 g., 0.60 mole) gave, on distillation through a Vigreux column, diethyl isopropenyl phosphate (VIII), 84 g., 80%, b.p. 98–101° (11 mm.), n^{25}_{D} 1.4187, and diethyl β-ketopropylphosphonate, 9.5 g., 9%, b.p. 87–97° (1.5 mm.), n^{25}_{D} 1.4324, with an infrared spectrum similar to that of the product (II) obtained from the reaction of triethyl phosphite and iodoacetone.

Treatment of diethyl isopropenyl phosphate with 2,4-dinitrophenylhydrazine in ethanol or in ethanol–acetic acid solution did not yield any derivative. When this reaction was carried out in methanol–sulfuric acid solution, yellow needles were obtained which, after two recrystallizations from ethanol, melted at 123–124.5° and did not depress the melting point of the 2,4-dinitrophenylhydrazone prepared from acetone.

Anal. Calcd. for $C_9H_{10}O_4N_4$: N, 23.5. Found: N, 23.3.

Ozonolysis of Diethyl Isopropenyl Phosphate.—A solution of VIII (508 mg., 2.62 mmoles) in 500 ml. of ethyl ace-

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(19) For the determination of the neutral equivalent, a weighed sample of the ester was hydrolyzed by refluxing overnight with 6 *N* hydrochloric acid, and most of the hydrogen chloride was removed by azeotropic distillation with two portions of benzene. The residue was diluted with water and titrated electrometrically. The titration curve found was that of phosphoric acid; the neutral equivalent was calculated on the basis of the alkali required to raise the *p*H from the first inflection point at 4.2 to the second inflection point at 8.5.

(20) D. P. Evans, W. C. Davies and W. J. Jones, *J. Chem. Soc.*, 1310 (1930).

tate was treated with ozone at −80° at the rate of 0.5 mmole per minute. After five minutes, unreacted ozone was present in the effluent gases whereupon ozonization was halted and the mixture concentrated to 20 ml. under reduced pressure. This residue was diluted to 250 ml. with water, and after standing for several days aliquot samples were removed and analyzed for formaldehyde. Colorimetric determination with chromotropic acid indicated a 14.6% yield of formaldehyde whereas gravimetric determination as the methone derivative gave a 12.2% recovery.

Diethyl Isopropyl Phosphate (IX) from VIII.—A solution of VIII (1.54 g., 7.9 mmoles) in 20 ml. of ethyl acetate was hydrogenated in the presence of 210 mg. of 10% palladium-on-charcoal. At the end of 42 minutes, 8.4 mmoles of hydrogen had been absorbed and further uptake ceased. After removal of the catalyst and the solvent, the residue was distilled to yield diethyl isopropyl phosphate (IX), 1.1 g., 70%, b.p. 84–86° (20 mm.), $n^{25}\text{D}$ 1.4038. This material is quite hygroscopic; a hydroxyl peak was observed in the infrared absorption spectrum unless determined in carbon tetrachloride solution immediately after drying over magnesium sulfate, in which case the infrared spectrum (characteristic peaks at 1167 and 1262 cm.$^{-1}$) was identical with that of a similarly dried solution of authentic diethyl isopropyl phosphate. Analytical results on a sample of the pure liquid IX dried with magnesium sulfate were not quite correct, but they were similar to those found with the authentic material (see below). Phosphorus analyses were low and varied widely on duplicate samples of this substance.

Anal. Calcd. for $C_7H_{17}O_4P$: C, 42.86; H, 8.67; neut. equiv., 196. Found: C, 41.50; H, 8.78; neut. equiv., 200.[19]

Diethyl Isopropyl Phosphate (IX) from Diethyl Phosphonate.[12]—A solution of diethyl phosphonate (13.8 g., 0.10 mole), dry isopropyl alcohol (20 ml.), bromotrichloromethane (20 ml.) and 2,6-lutidine (20 ml.) in 100 ml. of dry ether was allowed to stand overnight at room temperature whereupon a copious precipitate of amine hydrobromide was formed. This was removed by filtration, and the filtrate was washed with 15 ml. of water, dried and evaporated under reduced pressure. Distillation of the residue yielded diethyl isopropyl phosphate, 3.9 g., 24%, b.p. 101–103° (20 mm.), $n^{25}\text{D}$ 1.4042. The infrared spectrum of this compound (in CCl_4) showed characteristic peaks at 1167 and 1262 cm.$^{-1}$. As mentioned previously, because of the hygroscopic nature of this substance, it was necessary to dry the solution before determination of the spectrum, and the results obtained on microanalysis were not quite correct even after drying the sample with magnesium sulfate.

Anal. Calcd. for $C_7H_{17}O_4P$: C, 42.86; H, 8.67; P, 15.76; neut. equiv., 196. Found: C, 41.65; H, 8.92; P, 13.26; neut. equiv., 207.[19]

Diethyl Hydrogen Phosphate (X) from VIII.—Preliminary investigations of the hydrogenation of diethyl isopropenyl phosphate (VIII) using reduced platinum oxide in ethyl acetate indicated that two moles of hydrogen were absorbed to form a strongly acidic product. In one experiment VIII (186 mg., 0.96 mmole) in 15 ml. of ethyl acetate was hydrogenated using 45 mg. of platinum oxide, whereupon 1.69 mmoles of hydrogen were absorbed in 15 minutes. After filtration, the entire reduction mixture was titrated electrometrically with standard alkali to *p*H 7.9. In this way an equivalent weight of 202 was obtained for VIII as compared to the calculated value of 194.

To isolate the reduction product, a solution of VIII (3.5 g., 0.018 mole) in 35 ml. of absolute ethanol was hydrogenated in a Parr apparatus with 400 mg. of platinum oxide for 90 minutes. After filtration and evaporation of the solvent, the residue was distilled in a molecular still to yield diethyl hydrogen phosphate (X), 1.66 g., 60%, $n^{26}\text{D}$ 1.4170, reported[21] $n^{25}\text{D}$ 1.4152.

Anal. Calcd. for $C_4H_{11}O_4P$: C, 31.20; H, 7.14; P, 20.15. Found: C, 31.30; H, 7.37; P, 20.20.

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(21) A. D. F. Toy, This Journal, **70**, 3882 (1948).

CHICAGO 37, ILLINOIS

[Contribution from the Ben May Laboratory for Cancer Research and the Department of Biochemistry, University of Chicago]

Phosphonic Acids. V.[1] An Improved Method for the Preparation of Sodium Diethyl Phosphonate and a Study of its Comparative Reactivity with Alkyl Halides and *p*-Toluenesulfonates[2]

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Sodium diethyl phosphonate is prepared rapidly and conveniently by treatment of a solution of diethyl phosphonate with an excess of sodium hydride. In tetrahydrofuran solution, the relative reaction rates of primary alkyl halides and *p*-toluenesulfonates with sodium diethyl phosphonate are RBr > ROTs > RCl. The reaction of sodium diethyl phosphonate with trimethylene chlorobromide gives diethyl γ-chloropropylphosphonate, which on hydrolysis yields γ-chloropropylphosphonic acid.

Sodium diethyl phosphonate, or sodium diethyl phosphite, a reagent commonly used for the preparation of phosphonic acid esters, generally has been prepared[3] by treatment of a solution of diethyl phosphonate with either an equivalent amount of sodium ethoxide (or methoxide) or else with metallic sodium which dissolves with the evolution of hydrogen. Since alcohol and diethyl phosphonate probably do not differ greatly in their acid strengths the former method has the disadvantage that some sodium ethoxide may remain in the mixture either to compete with sodium diethyl phosphonate in its nucleophilic reactions or to react with the products formed. The latter procedure has the disadvantage that metallic sodium dissolves rather slowly in solutions of diethyl phosphonate so that many hours or even days may be required for completion of the reaction. Moreover, the dissolving metal acts as a reducing agent, and solutions of sodium diethyl phosphonate prepared in this way invariably are contaminated with phosphine compounds as indicated by the characteristic odor.[4]

It was found that the undesirable features of either procedure could be avoided by the use of sodium hydride as the basic reagent according to the equation

$$HPO(OEt)_2 + NaH \longrightarrow NaPO(OEt)_2 + {}^1/_2H_2$$

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[1] Paper IV, H. I. Jacobson, M. J. Griffin, S. Preis and E. V. Jensen, This Journal, **79**, 2608 (1957).

[2] This investigation was supported in part by a grant from the National Institutes of Health, Public Health Service (RG-3053).

[3] G. M. Kosolapoff, "The Organic Chemistry of Phosphorus," John Wiley and Sons, Inc., New York, N. Y., 1950, Ch. 7.

[4] P. Nylen, Dissertation, Uppsala, 1930, p. 32.