Experimental Section

General. All chemicals were reagent grade and were not further purified. Enzymes used in the assay of 1—acetate kinase (EC 2.7.2.1) and a commercial mixture of glucose 6-phosphate dehydrogenase (EC 1.1.1.49) and hexokinase (EC 2.7.1.1)—were obtained from Sigma Chemical Co. Anhydrous ammonia was obtained from Matheson, and was used directly from the tank without purification. Phosphoric acid (100%) was made by the slow addition of 191.5 g of phosphorus pentoxide to 500 g of stirred 85% phosphoric acid at −10 °C (ice/acetone bath). Water used in enzymatic assays was distilled twice, the second time using a Corning Model AG-1b distillation apparatus. Ultraviolet absorbance was measured using a Gilford Model 220 spectophotometer. A Radiometer Model PHM 62 pH meter was used to determine pH values.

Enzymatic Assay for AcP. The enzymatic assay used to determine the yield and purity of acetyl phosphate is that previously described.[4]

Diammonium Acetyl Phosphate. Ethyl acetate (2000 mL) and 100% phosphoric acid (294 g, 3.00 mol) were cooled in a 3-L flask to 0 °C in an ice bath. Acetic anhydride (551 g, 5.4 mol) was first cooled in an ice bath to 0 °C and then slowly added to the ethyl acetate/phosphoric acid mixture. The resulting solution was stirred at 0 °C for 3.7 h. A 5-L three-neck flask was fitted with a thermometer, a gas inlet tube, and an overhead stirrer. The stirrer shaft entered the flask through a fitting equipped with a side arm which served as a gas outlet. Methanol (2250 mL) was added, and anhydrous ammonia was allowed to enter with constant stirring. The flask was cooled to −30 °C in a dry ice/acetone bath, and the methanol was allowed to become saturated with ammonia (~30 min). The addition of ammonia was stopped, and the gas inlet tube was replaced with a 3-L addition funnel. The ethyl acetate/acetic anhydride/phosphoric acid mixture was placed in the addition funnel and slowly added to the vigorously stirred methanol solution. This addition took approximately 20 min, during which time the methanol solution rose in temperature to −10 °C. The fine solid which filled the flask was collected by suction filtration on a Büchner funnel. It was washed with 600 mL of methanol and then 600 mL of anhydrous ether. Final drying to constant weight under vacuum gave 524 g of solid. Enzymatic assay showed that the solid contained 86% diammonium acetyl phosphate (2.6 mol) by weight, corresponding to an 86% yield based on phosphoric acid. This material was stored at 0 °C and protected from atmospheric moisture.[4]

Registry No.—1, 55660-58-7; phosphoric acid, 7664-38-2; acetic anhydride, 108-24-7; ammonia, 7664-41-7.

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Facile Synthesis of 1,2-Oxaphosphol-3-ene Derivatives

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Received September 11, 1978

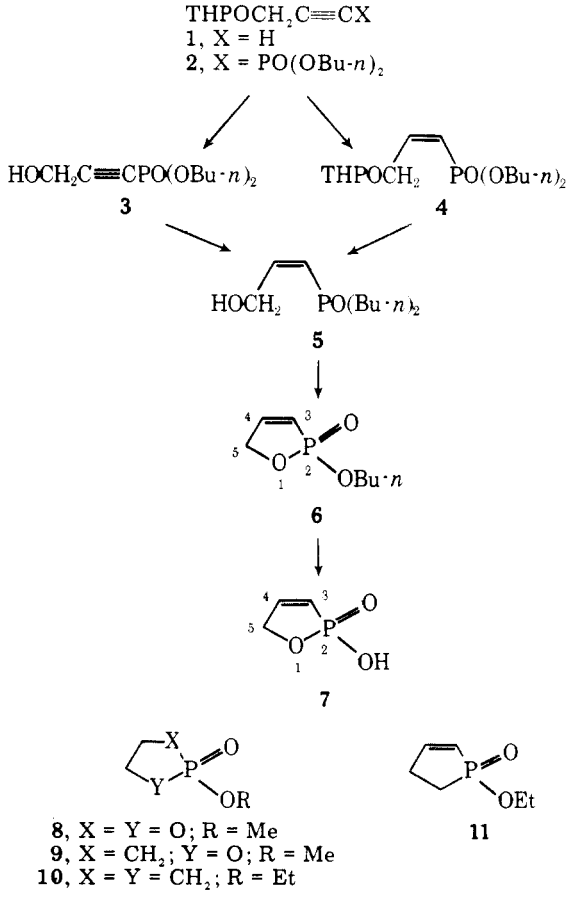
Although a large number of phosphorus-containing heterocycles are known, there have been relatively few 1,2-oxaphosphol-3-enes recorded in the literature. Surprisingly, all the known 1,2-oxaphosphol-3-enes carry at least one substituent on the ring carbon atom(s). A procedure involving acid-promoted cyclization of allenic phosphonic acid derivatives which was reported by Macomber[1] appears to be the most generally applicable method for the preparation of 1,2-oxaphosphol-3-enes. This method, however, failed to afford the "parent compound", **7**, even under forcing conditions.[1b] We wish to report here our findings that **7** can be synthesized very efficiently via its ester **6** under extremely mild conditions. The method includes two consecutive, hitherto undescribed, spontaneous reactions.

Propargyl alcohol tetrahydropyranyl ether, **1**, was treated with EtMgBr followed by $ClPO(OBu\text{-}n)_2$[2] in THF–benzene to afford the phosphonate **2** in 50% yield. Deprotection with TsOH in MeOH gave the desired alcohol **3** in 77% yield, which upon hydrogenation using $Pd\text{–}BaSO_4$ and quinoline in MeOH afforded the *cis*-olefin **5** in ca. 95% yield (by ^1H NMR). Column chromatography of crude **5** on silica gel using MeOH–Et_2O led to the isolation of a more polar material, to which structure **6** was assigned by spectroscopic and analytical data (see the Experimental Section). To our knowledge, this represents the first observation that a γ-hydroxy-α,β-unsaturated phosphonic acid derivative is cyclized to a 1,2-oxaphosphol-3-ene system. A clean spontaneous conversion of **5** to **6** was also observed when **5** was kept at room temperature for 3 days.

Interestingly, when **6** was allowed to stand at room temperature as a film under air for 2 days, it was spontaneously converted to a much more polar crystalline material.[3] The structure of this compound was established as **7** by spectroscopic and analytical data (see the Experimental Section).

The isolated yields of **6** from **3** and **7** from **6** were 83 and 95%, respectively.

Alternatively, **6** and **7** were synthesized from the intermediate **4** obtained from **2** in 93% yield by hydrogenation. Treatment of **4** with a catalytic amount of TsOH in CD_3OD at room temperature for 20 min yielded **6**, which upon addition of D_2O afforded **7** within 24 h at room temperature, quantitatively in both cases as monitored by ^1H NMR.



Quantitative conversion of **4** into **7** via **6** was also observed when **4** was treated with 0.5 N DCl–D_2O–CD_3OD at room temperature for 2 h (by ^1H NMR). The isolated yield of **7** from **4** by this latter method was 85%. It is interesting to note that **6** is hydrolyzed with exclusive ring retention under such mild conditions as described above since it is known that compounds **8** and **9** are hydrolyzed rapidly with 70% and nearly 100% ring opening, respectively, and that compounds **10** and **11** are hydrolyzed as slowly as their acyclic analogues.[4a]

In summary, we have described a facile synthesis of **6** by spontaneous or silica gel catalyzed cyclization of **5** and the synthesis of **7** by spontaneous or acid-catalyzed hydrolysis of **6**.

Experimental Section

The melting point was determined on a Yanagimoto micromelting point apparatus and is uncorrected. ^1H and ^{13}C NMR spectra of **7** were determined on a Jeol FX-100 spectrophotometer. All other ^1H NMR spectra were determined on a Hitachi R-24 spectrophotometer. Infrared spectra were obtained on a 215 Hitachi grating infrared spectrophotometer. Mass spectra were obtained on a Jeol JMS-OISG spectrometer. Elemental analyses were obtained on a Yanaco CHN Corder MT-2 instrument. Merck precoated silica gel $60F_{254}$ plates were used for TLC and visualization was performed by I_2 for all compounds and the molybdenum blue reagent[5] for **6** and **7**. Silica gel, 60–80 mesh, used for column chromatography, was a product of Kanto Chemical Co., Inc., Tokyo.

Di-*n*-butyl 3-(2-Tetrahydropyranyloxy)-1-propynylphosphonate (2). A solution of **1** (42 g, 0.3 mol) in THF (120 mL) was added dropwise to a stirred solution of EtMgBr (0.3 mol) in THF (240 mL) at 0–5 °C under N_2 and the mixture was stirred at room temperature for 30 min. To this mixture was added a solution of $ClPO(OBu\text{-}n)_2$[2] (68.6 g, 0.3 mol) in benzene (360 mL) dropwise, keeping the temperature below 40 °C. After being stirred at room temperature for a further 3 h, the mixture was worked up in the usual manner. The crude product was chromatographed (silica gel, 200 g; Et_2O–hexane, 1:1) to afford **2** (49.7 g, 50%) as an oil: IR (neat) 2220 cm^{-1}; ^1H NMR ($CDCl_3$) δ ~3.6 (2 H, m, OCH_2 of THP), 4.05 (4 H, dt, $^3J_{PH}$ = 7 Hz, $^3J_{HH}$ = 6 Hz, OCH_2 of *n*-Bu), 4.31 (2 H, d, $^4J_{PH}$ = 4 Hz, 3-H), 4.74 (1 H, m, acetal H).

Di-*n*-butyl 3-Hydroxy-1-propynylphosphonate (3). A solution of **2** (20 g, 60 mmol) and TsOH (100 mg) in MeOH (300 mL) was heated at 55 °C for 1 h. MeOH was removed at room temperature and the residue was dissolved in Et_2O (200 mL), washed with 5% $NaHCO_3$ solution followed by brine, and dried ($MgSO_4$) and the solvent was evaporated. The residue was chromatographed (silica gel, 200 g; MeOH–Et_2O, 1:49) to afford **3** (11.5 g, 77%) as an oil: IR (neat) 3380, 2220 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.01 (4 H, dt, $^3J_{PH}$ = 7.5 Hz, $^3J_{HH}$ = 6 Hz, OCH_2 of *n*-Bu), 4.23 (2 H, d, $^4J_{PH}$ = 4 Hz, 3-H).

Di-*n*-butyl *cis*-3-(2-Tetrahydropyranyloxy)-1-propenylphosphonate (4). Compound **2** (6.64 g, 20 mmol) was hydrogenated in the same manner as described for the preparation of **5** from **3** (see below). The crude product was chromatographed (silica gel, 120 g; Et_2O–hexane, 2:1) to afford **4** (6.21 g, 93%) as an oil: IR (neat) 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ ~3.6 (2 H, m, OCH_2 of THP), 4.02 (4 H, br q, $^3J_{PH} \simeq {}^3J_{HH} \simeq$ 6 Hz, OCH_2 of *n*-Bu), 4.58 (3 H, m, acetal H and 3-H), 5.63 (1 H, ddt, $^3J_{PH}$ = 19 Hz, $^3J_{HH}$ = 14 Hz, $^4J_{HH}$ = 1.5 Hz, 1-H), 6.60 (1 H, ddt, $^3J_{PH}$ = 50 Hz, $^3J_{HH_1}$ = 14 Hz, $^4J_{HH_3}$ = 5.5 Hz, 2-H).

Di-*n*-butyl *cis*-3-Hydroxy-1-propenylphosphonate (5). A mixture of **3** (12.82 g, 51.7 mmol), 5% Pd–$BaSO_4$ (0.4 g), quinoline (0.4 g), and MeOH (100 mL) was shaken under H_2 at room temperature and at atmospheric pressure until 1 equiv of H_2 was absorbed. The mixture was filtered and evaporated to give crude **5** as an oil (ca. 95% pure by ^1H NMR): IR (neat) 3400, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.03 (4 H, dt, $^3J_{PH}$ = 7 Hz, $^3J_{HH}$ = 6 Hz, OCH_2 of *n*-Bu), 4.48 (2 H, m, 3-H), 5.57 (1 H, ddt, $^2J_{PH}$ = 17 Hz, $^3J_{HH}$ = 14 Hz, $^4J_{HH}$ = 1.5 Hz, 1-H), 6.70 (1 H, ddt, $^3J_{PH}$ = 53 Hz, $^3J_{HH_1}$ = 14 Hz, $^3J_{HH_3}$ = 5.5 Hz, 2-H).

2-*n*-Butyloxy-2-oxo-1,2-oxaphosphol-3-ene (6). Crude **5** obtained from **3** (1.24 g, 5 mmol) as above was percolated through a silica gel (30 g) column using MeOH–Et_2O (1:49) as an eluent to afford pure **6** (0.73 g, 83% from **3**) as an oil: TLC R_f 0.70 (BuOH–AcOH–H_2O, 3:1:1); IR (neat) 3080, 1590 cm^{-1}; mass spectrum *m/e* 176 (M^+); ^1H NMR ($CDCl_3$) δ 3.95 (2 H, dt, $^3J_{PH}$ = 9 Hz, $^3J_{HH}$ = 6.5 Hz, OCH_2 of *n*-Bu), 4.75 (2 H, d of br t, $^3J_{PH}$ = 6.5 Hz, $^3J_{HH} = {}^4J_{HH}$ = 2 Hz, 5-H),[7] 6.10 (1 H, ddt, $^2J_{PH}$ = 34 Hz, $^3J_{HH}$ = 9 Hz, $^4J_{HH}$ = 2.5 Hz, 3-H), 7.15 (1 H, ddt, $^3J_{PH}$ = 47 Hz, $^3J_{HH_3}$ = 9 Hz, $^3J_{HH_5}$ = 1.5 Hz, 4-H). Anal.[8] Calcd for $C_7H_{13}O_3P$: C, 47.73; H, 7.44. Found: C, 46.96; H, 7.46.

2-Hydroxy-2-oxo-1,2-oxaphosphol-3-ene (7). (A) Compound **6** (0.242 g, 1.38 mmol) was kept in a vial as a ca. 1 mm thick film at room temperature under air for 48 h. Crystals separated were washed with Et_2O–hexane (2:1) to afford pure **7** (0.166 g, 95%): mp 110–111 °C; TLC R_f 0.07 (BuOH–AcOH–H_2O, 3:1:1); IR (Nujol) 3500–2000, 3100, 1590, 1250–1200, 1010 cm^{-1}; mass spectrum *m/e* 120 (M^+); ^1H NMR ($Me_2SO\text{-}d_6$)[9,10] δ 4.67 (2 H, d of br t, $^3J_{PH}$ = 5.9 Hz, $^3J_{HH} \simeq {}^4J_{HH} \simeq$ 2 Hz, 5-H),[11] 6.30 (ddt, $^2J_{PH}$ = 34.8 Hz, $^3J_{HH}$ = 8.5 Hz, $^4J_{HH}$ = 2.4 Hz, 3-H), 7.14 (ddt, $^3J_{PH}$ = 45.6 Hz, $^3J_{HH_3}$ = 8.5 Hz, $^3J_{HH_5}$ = 1.6 Hz, 4-H); ^{13}C NMR ($CDCl_3$)[10] δ 147.5 ($^2J_{PC}$ = 15.9 Hz, 4-C), 118.2 ($^1J_{PC}$ = 157.5 Hz, 3-C), 70.2 ($^2J_{PC}$ = 13.4 Hz, 5-C). Anal. Calcd for $C_3H_5O_3P$: C, 30.01; H, 4.20. Found: C, 30.05; H, 4.20. Recrystallization from $CHCl_3$ did not alter the physical constants.

(B) A solution of **4** (3.34 g, 10 mmol) in 0.5 N HCl in H_2O–MeOH (1:4, 15 mL) was stirred for 2 h at room temperature. The solvent was evaporated at room temperature and the residue was recrystallized from $CHCl_3$ to afford **7** (1.02 g, 85%). The physical constants were the same as given above.

Acknowledgment. We thank Dr. T. Suzuki and Miss K. Koizumi for taking the ^1H and ^{13}C NMR spectra of **7**, Mrs. T. Yamashiro for mass spectral measurements, and Miss Y. Nakajo for elemental analyses.

Registry No.—**1**, 6089-04-9; **2**, 68492-50-2; **3**, 68492-51-3; **4**, 68492-52-4; **5**, 68492-53-5; **6**, 68492-54-6; **7**, 68492-55-7; phosphorochloridic acid dibutyl ester, 819-43-2.

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(7) The two protons seem to have identical chemical shifts with each other since the signal shape is the same as that of the corresponding protons in **7**. The appearance of the signal as a double triplet is attributed to the inadequate resolution.
(8) The slight difference between the calculated and experimental values may be due to some hydrolysis of **6** by moisture during handling of the sample.
(9) For the predicted ^1H NMR values, see ref 1b.
(10) The assignment was confirmed by ^1H–^1H and ^1H–^{13}C decoupling experiments.
(11) The signal failed to give a double quartet because of inadequate resolution.

Synthesis of 12-Fluoro-7-methylbenz[*a*]anthracene and 7-Fluoro-12-methylbenz[*a*]anthracene

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Received August 14, 1978

7-Methylbenz[*a*]anthracene (**1**) has long been recognized to be the most carcinogenic monomethylbenz[*a*]anthracene.[3] The substitution of a methyl group at position 12 of **1** to produce 7,12-dimethylbenz[*a*]anthracene (DMBA) (**2**) leads to the most carcinogenic dimethylbenz[*a*]anthracene hydrocarbon known. For some time[4] we have been concerned with understanding why the methyl group at 12 should increase the activity of **1**. Three explanations may be considered: 1, the methyl at 12 is metabolized to give a more potent carcinogen; 2, the methyl at 12 blocks a detoxification mechanism which occurs at position 12; and 3, the steric effect of the 12-methyl group causes sufficient intramolecular overcrowding that the noncoplanar[5] DMBA is more easily metabolized to the ultimate carcinogen.

0022-3263/79/1944-0866$01.00/0