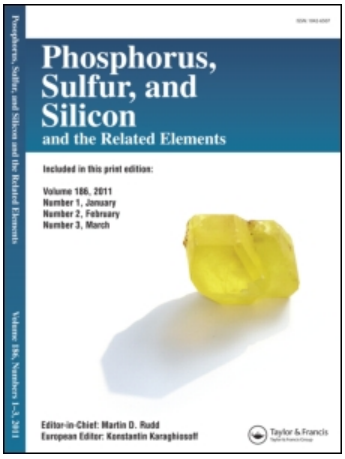

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TWO-STEP 3-PHOSPHOLENE TO PHOSPHORINONE TRANSFORMATION

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TWO-STEP 3-PHOSPHOLENE TO PHOSPHORINONE TRANSFORMATION

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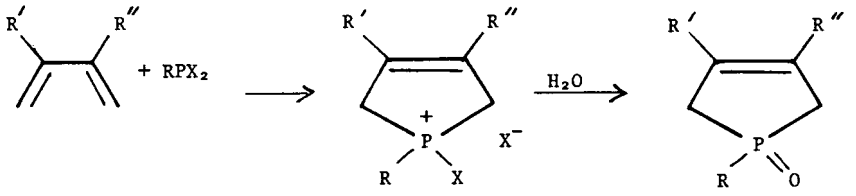
Ozonolysis of 3-phospholene oxides cleanly opens the double bond and provides bis(β-oxoalkyl) phosphine oxides. Aldol condensation can be effected with p-toluenesulfonic acid to give 1,6-dihydro-3(2H)phosphorinone derivatives. The four new members of this family were characterized by ^{31}P and ^{13}C NMR spectroscopy.

The highly versatile McCormack cycloaddition of dienes and phosphorus(III) halides has made 3-phospholene derivatives among the most readily accessible of heterocyclic phosphorus compounds.[1]



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We have devised a two-step method (Scheme 1) for the transformation of phospholenes into derivatives of the phosphorinane ring system. The products are particularly valuable since the synthetic method creates in the ring the reactive α,β-unsaturated ketone function.

In the first step of the transformation, the double bond in 3-phospholene oxides (**1**) is opened by ozonolysis at −78°. The ozonides are reduced with trimethyl phosphite, providing bis(β-oxoalkyl) derivatives (**2**) in good yield. Four substances of this type have been prepared; only one (**2c**) was previously known.[4] Other synthetic methods for generating such phosphorus compounds include the hydration of bis-acetylenic derivatives, either directly[2] or through the bis-enamines arising from addition of amines,[3] or the hydrolysis of 1,4-oxaphosphorin derivatives.[4] Our method has the valuable feature of providing products with two different carbonyl-containing substituents on phosphorus, which result when the 3-phospholene derivative is not symmetrically substituted. In two of the β-oxoalkyl phosphine oxides (**2c**, **2d**), the carbonyl group is present in the ketonic form, and these proved to be easily purified and thermally stable. Compounds **2a** and **2b** had one carbonyl substituent

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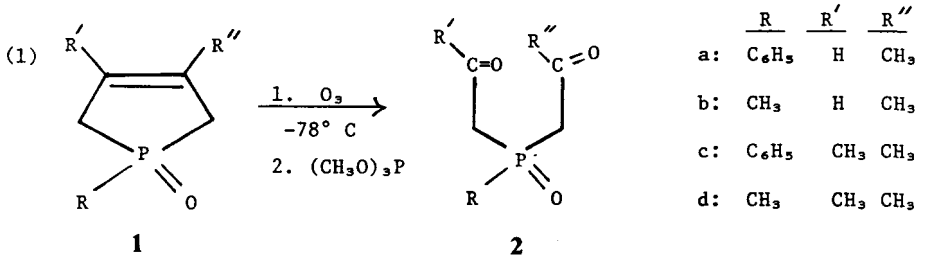

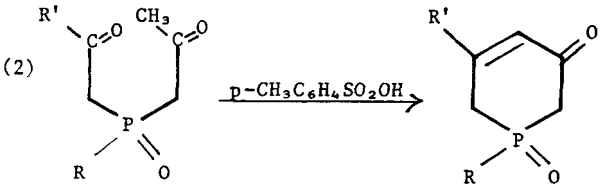

2a, R=C_6H_5, R'=H

2b, R=CH_3, R'=H

2c, R=C_6H_5, R'=CH_3

2d, R=R'=CH_3

3a, R=C_6H_5, R'=H (52% from **1a**)

3b, R=CH_3, R'=H (36% from **1b**)

3c, R=C_6H_5, R'=CH_3 (99% from **2c**)

3d, R=R'=CH_3 (98% from **2d**)

SCHEME 1

as an aldehyde, and these compounds were much less stable. They were subjected to the second step of the synthesis without full characterization.

Ozonolysis of 3-phospholene derivatives is not a new reaction; it was first used[5] in 1963 in early work concerned with the location of the double bond in phosphinic acids obtained from McCormack cycloadditions, and later[6] to create large phosphorus heterocycles by cleaving a transannular double bond in 3-phospholene oxides with fused cycloalkane rings. Ozonolysis has never before been exploited as a synthetic method in monocyclic phospholene oxide chemistry, however.

The second step of the phosphorinone synthesis involves aldol condensation of the bis(β-oxoalkyl) derivatives (Scheme 1, reaction 2). This is best accomplished with the use of an acid catalyst in the proper solvent. For aldehydes **2a** and **2b** p-toluenesulfonic acid in benzene gave the best results. The diketones **2c** and **2d** failed to condense in the medium, but replacement of the benzene with acetic acid gave nearly quantitative yields of phosphorinones after a several-day reaction period. Basic catalysts such as lithium diisopropylamide in THF, or NaOH in ethanol or benzene, were not effective for cyclizing the diketones. All phosphorinones were crystalline solids, and were fully characterized by ^1H, ^{31}P, and ^{13}C NMR and IR spectroscopy. In two cases (**3b** and **3d**) high field (250 MHz) ^1H NMR spectra were obtained to provide resolution of the signals arising from the two CH_2 groups (downfield, $CH_2C{=}O$; upfield, $CH_2C{=}C$). In these groups the protons are non-

equivalent and also are coupled to ^{31}P, giving second-order spectra. In **3b**, the upfield signal shows additional splitting from the adjacent olefinic proton (HC-5) which is an aid in its assignment. The C-5 proton also gives a complex signal; it is well separated by large coupling (28 Hz) with ^{31}P into two multiplets, each with splitting by H_2C-6 and HC-4. In **3d**, the two CH_2 multiplets were not completely resolved, although the absence of the proton on C-5 led to a less complex multiplet for the upfield region. The assignments of the CH_2 groups are the same as made in an earlier report on phosphorinones.[7]

The phosphorinone system was previously synthesized by Märkl and coworkers[7] using acid hydrolysis of 1,4-oxaphosphorin-4-oxides; bis(β-ketoalkyl) compounds have been suggested as intermediates which then are cyclized by aldol condensation. These products always bear 4- or 4,5-substituents as a consequence of the synthetic method used for the 1,4-oxaphosphorin synthesis.[8] In order to demonstrate the special utility of our new approach, we purposely synthesized C-unsubstituted derivatives **3a, b** since these are not available by the other route. Given the wide scope of the McCormack cycloaddition reaction, our two-step method has the potential of providing a great variety of phosphorinones.

EXPERIMENTAL[9]

Conversion of 3-Methyl-1-phenylphospholene-1-oxide (**1a**) *to 1,6-Dihydro-1-phenyl-3(2H)phosphorinone-1-oxide* (**3a**). Ten g (0.052 mol) of **1a** in 125 ml of methanol–methylene chloride (1 : 1) was treated with ozone at −78° until the light blue color of excess ozone appeared. Nitrogen was passed through the solution to remove excess ozone, and then 7.1 g (0.057 mol) of trimethyl phosphite (Aldrich, 99 + %) was added slowly at −78°. The solution was stirred for 5 min at −78° and then allowed to warm to room temperature. The solvent was removed by rotary evaporation to yield a clear oil containing **2a** and trimethyl phosphate. For **2a**, ^{31}P NMR ($CDCl_3$) δ +28.7; ^1H NMR (80 MHz, $CDCl_3$) δ 2.3 (s, $-CH_3$), 3.35–3.90 (m, 4 H, CH_2), 7.4–7.9 (m, $P-C_6H_5$), 9.65–9.85 (m, —CHO).

To the crude **2a** was added 500 ml of benzene and 0.5 g of p-toluenesulfonic acid. The solution was refluxed for 48 h using a Soxhlet extractor containing molecular sieves (5 Å) and Na_2SO_4. The benzene was decanted and rotary-evaporated to give an oil that partially crystallized. The mass was washed with acetone and chromatographed on silica gel (5% MeOH–$CHCl_3$) to yield 5.6 g of **3a** (52.2% from **1a**); m.p. 170–171° after recrystallization from acetone; ^{31}P NMR ($CDCl_3$) δ +32.2; ^{13}C NMR ($CDCl_3$) δ 28.9 ($^1J_{PC}$ = 65.9 Hz, C-5), 44.0 ($^1J_{PC}$ = 53.7 Hz, C-2), 128.8 ($^3J_{PC}$ = 12.2 Hz, C-*meta*), 129.8 ($^2J_{PC}$ = 9.8 Hz, C-*ortho*), 130.7 ($^1J_{PC}$ = 101.3 Hz, C-*ipso*), 132.2 ($^3J_{PC}$ = 3.7 Hz, C-4), 132.6 ($^4J_{PC}$ = 2.5 Hz, C-*para*), 140.2 ($^2J_{PC}$ = 3.7 Hz, C-5), 191.4 ($^2J_{PC}$ = 3.7 Hz, C-3); ^1H NMR (80 MHz, $CDCl_3$) δ 2.9–3.3 (m, 2 H, H_2C-6), 3.3–3.6 (m, 2 H, H_2C-2), 6.25 (d of d, 12 Hz ($^3J_{HH}$) and 2.4 Hz, =CHCO—), 6.5–7.2 (m, —CH=), 7.3–7.9 (m, $-C_6H_5$); IR (nujol) $\nu_{C=O}$ 1670 cm^{-1}.

Anal. Calcd for $C_{11}H_{11}O_2P$: C, 64.06; H, 5.38; P, 15.03. Found: C, 64.29; H, 5.37; P, 14.93.

Conversion of 1,3-Dimethyl-3-phospholene-1-oxide (**1b**) *to 1,6-Dihydro-1-methyl-3(2H)phosphorinone-1-oxide* (**3b**). Ten g (0.0768 mol) of **1b** was ozonized according to the procedure for **1a**. The solvent was removed to yield a clear oil (**2b**) used directly in the synthesis of **3b**. To the crude **2b** was added 500 ml of benzene and 0.5 g of p-toluenesulfonic acid. The solution was refluxed for 48 h using a Soxhlet extractor containing molecular sieves 5A and Na_2SO_4. The benzene was decanted and rotary-evaporated to give an oil that partially crystallized. The mass was washed with acetone and chromatographed on silica gel (5% MeOH–$CHCl_3$) to yield 4.0 g **3b** (36.1% from **1b**); m.p. 140–141° after recrystallization from acetone; ^{31} P NMR ($CDCl_3$) δ + 39.3; ^{13}C NMR ($CDCl_3$) δ 13.5 ($^1J_{PC}$ = 69.6 Hz, CH_3), 29.2 ($^1J_{PC}$ = 64.7 Hz, C-6), 44.9 ($^1J_{PC}$ = 51.3 Hz, C-2), 131.7 ($^3J_{PC}$ = 3.7 Hz, C-4), 140.2 ($^2J_{PC}$ = 3.7 Hz, C-5), 192.0 ($^2J_{PC}$ = 2.5 Hz, C-3); ^1H NMR (250 MHz, $CDCl_3$), δ 1.52 (d, $^2J_{PH}$ = 13.3 Hz, $P-CH_3$), 2.7–3.0 (m, 2 H, H_2C-6), 3.1–3.3 (m; 2 H, H_2C-2), 6.15 (d of d, 13.0 Hz, ($^3J_{HH}$) and 2.4 Hz, HC-4), 6.5–7.1 (m with $^3J_{PH}$ = 28 Hz, HC-5); IR (nujol)$\nu_{C=O}$ 1670 cm^{-1}.

Anal. Calcd for $C_6H_9O_2P$: C, 49.99; H, 6.29; P, 21.50. Found: C, 49.98; H, 6.27; P, 21.17.

Bis(2-oxopropyl)phenylphosphine Oxide (**2c**). A sample of 3.0 g (0.0145 mol) of **1c** was ozonized according to the procedure for **1a**. The solvent was removed by rotary evaporation to give a clear oil that

partially crystallized upon standing. The mass was washed with cold ether and recrystallized from ethyl acetate–hexane; yield 2.3 g (66.7%), m.p. 74.0–75.5°; recrystallized from $CHCl_3$–hexane, m.p. 74.0–75.5° (lit.[4] m.p. 130°; the cause for the discrepancy is not known); ^{31}P NMR ($CDCl_3$) δ +28.9; ^{13}C NMR ($CDCl_3$) δ 32.8 (s, CH_3), 46.4 ($^1J_{PC}$ = 59.1 Hz, CH_2), 128.7 ($^3J_{PC}$ = 12.1 Hz, C-*meta*), 130.3 ($^2J_{PC}$ = 9.4 Hz, C-*ortho*), 132.5 ($^4J_{PC}$ = 2.8 Hz, C-*para*), 201.2 ($^2J_{PC}$ = 6.7 Hz, C=O); ^1H NMR (80 MHz, $CDCl_3$) δ 2.29 (s, 6 H, CH_3), 3.45 (d, $^2J_{PH}$ = 14.5 Hz, 4 H, CH_2), 7.6 (m, C_6H_5).

Anal. Calcd for $C_{12}H_{15}O_3P$; C, 60.50; H, 6.34; P, 13.00. Found: C, 60.70; H, 6.17; P, 12.89.

1,6-Dihydro-1-phenyl-5-methyl-3(2H)phosphorinone-1-oxide (**3c**). To 0.60 g (0.0025 mol) of **2c** was added 50 ml of glacial acetic acid and 0.03 g of p-toluenesulfonic acid. The solution was refluxed for six days. The solvent was rotary-evaporated to give a yellow oil. Chromatography on silica gel (5% MeOH–$CHCl_3$) yielded 0.55 g (99%) of **3c**; m.p. 134–135°C after recrystallization from ethyl acetate–hexane; ^{31}P NMR ($CDCl_3$) δ +32.3; ^{13}C NMR ($CDCl_3$) δ 26.7 ($^3J_{PC}$ = 12.2 Hz, C—CH_3), 33.6 ($^1J_{PC}$ = 65.9 Hz, C-6), 41.9 ($^1J_{PC}$ = 56.2 Hz, C-2), 128.6 ($^3J_{PC}$ = 11.0 Hz, C-*meta*), 128.7 (s, C-4), 129.6 ($^2J_{PC}$ = 9.8 Hz, C-*ortho*), 132.4 ($^4J_{PC}$ = 2.4 Hz, C-*para*), 152.6 ($^2J_{PC}$ = 2.4 Hz, C-5), 190.6 (s, C-3); ^1H NMR (80 MHz, $CDCl_3$) δ 2.1 (s, C—CH_3), 2.9–3.2 (m, 2 H, H_2C-6), 3.2–3.5 (m, 2 H, H_2C-2), 6.2 (s, HC-4), 7.3–7.9 (m, —C_6H_5); IR (nujol) $\nu_{C=O}$ 1660 cm^{-1}.

Anal. Calcd for $C_{12}H_{13}O_2P$: C, 65.45; H, 5.95. Found: C, 65.54; H, 5.95.

Bis(2-oxopropyl)methylphosphine Oxide (**2d**). A sample of 2.0 g (0.0139 mol) of **1d** was ozonized according to the procedure for **1a**. The solvent was removed by rotary evaporation to yield a clear oil that was dissolved in 50 ml of $CHCl_3$. The solution was extracted with 50 ml of H_2O. The H_2O layer was concentrated to dryness and the residue redissolved in $CHCl_3$ and dried (Na_2SO_4). Removal of solvent yielded 2.1 g (86.1%) of a clear oil that crystallized in Dry Ice; approximate m.p. 31–33° (hygroscopic); ^{31}P NMR ($CDCl_3$) δ +38.4; ^{13}C NMR ($CDCl_3$) δ 15.9 ($^1J_{PC}$ = 71.2 Hz, P—CH_3), 32.8 (s, C—CH_3), 46.0 ($^1J_{PC}$ = 59.1 Hz, CH_2), 202.2 ($^2J_{PC}$ = 5.4 Hz, C=O); IR (neat) $\nu_{C=O}$ 1710 cm^{-1}.

Anal. Calcd for $C_7H_{13}O_3P$: P, 17.58. Found: P, 17.30.

1,6-Dihydro-1,5-dimethyl-3(2H)phosphorinone-1-oxide (**3d**). To 4.9 g (0.0278 mol) of **2d** was added 150 ml of glacial acetic acid and 0.25 g of p-toluenesulfonic acid. The solution was refluxed for two days. The solvent was rotary-evaporated to give a yellow oil. Chromatography on silica gel (8% MeOH–$CHCl_3$) yielded 4.3 g (98%) of **3d**; m.p. 68–70°C (hygroscopic) after recrystallization from ethyl acetate–hexane; ^{31}P NMR ($CDCl_3$) δ +40.2; ^{13}C NMR ($CDCl_3$) δ 13.2 ($^1J_{PC}$ = 70.8 Hz, P—CH_3), 26.7 ($^3J_{PC}$ = 12.2 Hz, C—CH_3), 33.4 ($^1J_{PC}$ = 64.7 Hz, C-6), 42.1 ($^1J_{PC}$ = 54.9 Hz, C-2), 128.2 (s, C-4), 152.9 (s, C-5), 191.1 (s, C-3); ^1H NMR (250 MHz, $CDCl_3$) δ 1.56 (d, $^2J_{PH}$ = 12.8 Hz, P—CH_3), 2.1 (s, C—CH_3), 2.6–3.0 (m, 2 H, H_2C-6), 3.1–3.2 (m, 2 H, H_2C-2), 6.1 (s, HC-4); IR (nujol) $\nu_{C=O}$ 1660 cm^{-1}.

Anal. Calcd for $C_7H_{11}O_2P$: C, 53.17; H, 7.01; P, 19.59. Found: C, 53.36; H, 7.10; P, 19.39.

ACKNOWLEDGMENT

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7. G. Märkl and K. Hock, *Chem. Ber.*, **116**, 1756 (1983) and earlier papers.
8. The quaternary salts formed from bis-(1-propynyl)-*tert*-butylphosphine with various (α-bromomethyl)ketones undergo cyclization *via* the enol form; basic hydrolysis causes elimination of the remaining propynyl group to give the phosphine oxide.

9. Proton NMR spectra were obtained on IBM NR-80 and Bruker WM-250 spectrometers, using tetramethylsilane as internal standard. Phosphorus-31 FT spectra were obtained on a JEOL FX-90Q spectrometer at 36.2 MHz, using 85% H_3PO_4 as external standard with an internal deuterium lock. Positive shifts are downfield of the reference. Carbon-13 spectra (FT) were obtained on the same instrument at 22.5 MHz with TMS as internal standard. Broad-band noise-decoupling was employed on all ^{13}C and ^{31}P spectra. Melting points were taken on a Mel-Temp apparatus and are corrected. Elemental analyses were performed by MHW Laboratories, Phoenix, AZ.