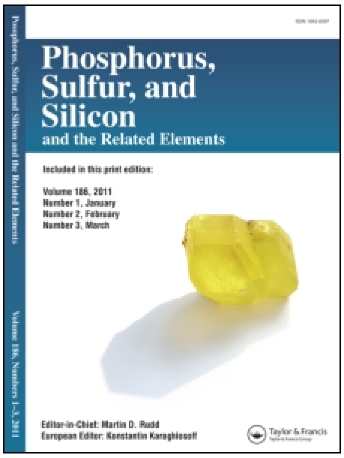

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Synthesis of New Benzoxaphosphole Derivatives from the Reaction of Dialkylphosphonates and Trisdialkylaminophosphines with 2,6-Bis(benzylidene)cyclohexanones

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*The reaction of 2,6-bis(benzylidene)cyclohexanones with dialkylphosphonates and tris(dialkylamino)phosphines afforded the new benzoxaphosphole derivatives (**5a–5d**) and (**9a–9f**). The biological activity of the newly synthesized compounds was also examined. Possible reaction mechanisms are considered, and the structural assignments are based on analytical and spectroscopic results. The structure of the new benzoxaphosphole **5a** was confirmed by a single crystal X-ray determination.*

Keywords Benzoxaphosphole; 2,6-bis(benzylidene)cyclohexanones; dialkylphosphonates; tris(dialkylamino)phosphonates.

INTRODUCTION

The increasing number of resistant bacterial strains, especially the highly resistant β-lactamase producing *Staphylococcus aureus* and Gram-negative strains, requires the development of new effective chemotherapeutic agents of low toxicity. α,β-Unsaturated ketones are known to possess antimicrobial effects.[1] This, together with our interest in organophosphorus chemistry,[2–9] has encouraged the synthesis of new organophosphorus compounds incorporating important nuclei that may possibly lead to further biological activity. The present study deals with the reaction of dialkylphosphonates **1a–1b** and tris(dialkylamino)phosphines **2a–2b** with 2,6-bis(benzylidene)cyclohexanones **3a–3c** (Scheme 1).

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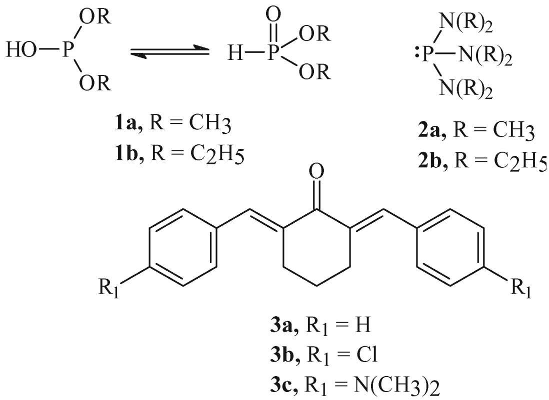
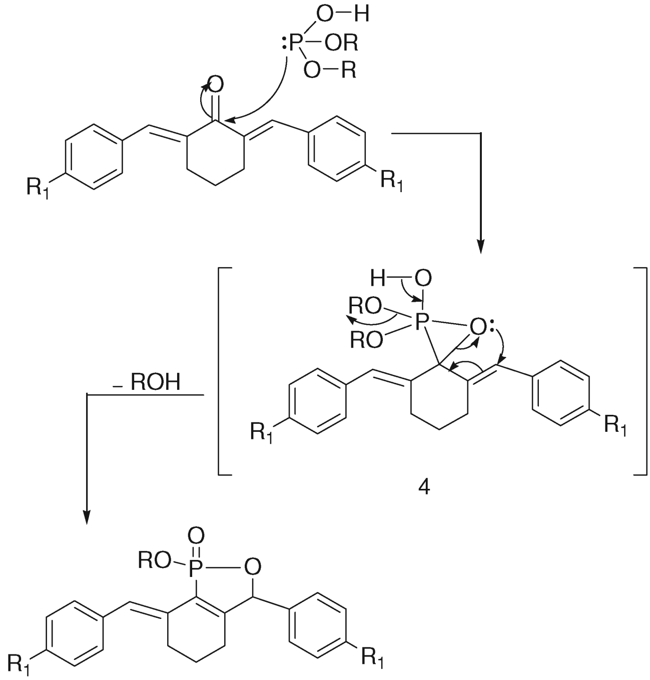


SCHEME 1

RESULTS AND DISCUSSION

We have found that 2,6-dibenzylidene cyclohexanone **3a** reacts with dimethylphosphonate **1a** in refluxing toluene for 10 h to give colorless crystals formulated as (7)-1-methoxy-3-phenyl-7-(phenylmethylidene)-1,3,4,5,6,7-hexahydro-2,1-benzoxaphosphole-1-oxide (**5a**) (Scheme 2). Compound **5a** is chromatographically pure and possesses a sharp melting point. The assigned oxaphosphole structure **5a** is based on the X-ray structural analysis, together with correct microanalysis, IR, ^{1}H, ^{13}C, ^{31}P NMR, and mass spectral data. The IR spectrum of compound **5a** reveals the absence of a carbonyl absorption, which is recorded with **3** at 1675 cm^{-1}. The spectrum also lacks the characteristic absorption band attributable to the stretching frequency of an enolate carbonyl function.[10] In addition, it exhibits intense bands corresponding to the P=O and P-O-(alkyl) stretching vibrations.[11] The ^{1}H NMR of **5a** gives signals at 3.86 ppm (3H, d, $^{3}J_{HP}$ = 11.87 Hz) for the methoxy group attached to phosphorus, two triplets at 2.16 and 1.88 ppm and a multiplet at 1.72 ppm for the **6** methylene protons, a singlet at 5.64 ppm for the CH proton of cyclic oxaphosphole, 6.70 for =CH, and multiplets at 7.26–7.39 ppm (10H, m, Ar). The ^{31}P NMR measurement of **5a** supports the oxaphosphole structure; it exhibits a sharp signal at δ = 37.62. The mass spectrum of **5a** gives a prominent peak at m/e 352 (M^{+}, 100%). In order to identify unambiguously the structure of the reaction product **5a,** an X-ray structure determination[12–15] of crystalline **5a** was performed (Figure 1, Tables I and II).

Similarly, diethylphosphonate **1b** reacts with **3a** to give adduct **5b** in 78% yield (Scheme 2). Structure **5b** was deduced from correct microanalysis, IR, ^{1}H, ^{13}C NMR, and MS spectral data (cf. the Experimental



5a, R=CH_3 , R_1= H
5b, R = C_2H_5 , R_1 = H
5c, R = CH_3 , R_1 = Cl
5d, R = C_2H_5 , R_1 = Cl

SCHEME 2

section). The reaction of 2,6-bis(4-chlorobenzylidene)cyclohexanone (**3b**) with dialkylphosphonates **1a** and **1b** was also investigated. We found that the reaction of **1a** and **1b** with **3b**, in dry toluene, proceeds at reflux temperature to give pure adducts formulated as **5c** and **5d** (Scheme 2). Structure **5c** and **5d** were substantiated on the basis of their elemental analysis, IR, ^{1}H, ^{13}C NMR, and mass spectral data (cf. the Experimental section).

We propose the reaction course depicted in Scheme 2 to account for these interesting results. The reaction, which is presumably initiated by a nucleophilic attack of the phosphite-phosphorus on the most reactive center carbonyl group of **3**, leads to the intermediate compounds (**4**), which undergoes cyclization followed by molecular rearrangements and loss of an alcohol molecule to give compounds (**5**) (Scheme 2).

TABLE I Crystal Structure and Data Refinement Parameters

Compound	**5a**	**10**
Empirical formula	$C_{21}H_{21}O_3P$	$C_{20}H_{19}O_3P$
Formula weight	352.370	338.34
Crystal system/space group	Monoclinic	Triclinic
a / Å	10.6510 (4)	9.6104(5)
b / Å	11.4099 (5)	9.6923(5)
c / Å	15.4764 (8)	10.4619(6)
α / °	90.00°	109.231(3)
β / °	101.355 (2)°	101.292(3)
γ / °	90.00°	99.214(2)
V / Å^3	1843.98 (14)	875.35(8)
Z	4	2
D_{calc} (g/cm^3)	0.00126	0.001386
μ (mm^{-1})	0.16	0.17
Crystal size (mm)	0.10 × 0.10 × 0.12	0.17 × 0.10 × 0.10
Color / Shape	Colorless/prismatic	Colorless/needles
Temp (K)	298	298
Theta range for collection	2.910–25.028 ^{0}	2.910–27.485°
Reflections collected	5439	5029
Independent reflections	3543	4402
Data/restraints/parameters	226	217
Goodness of fit on F^2	0.042	0.049
Final R indices [I > 2σ(I)]	R_{int} 0.031	R_{int} 0.035
R indices (all data)	0.090	0.122

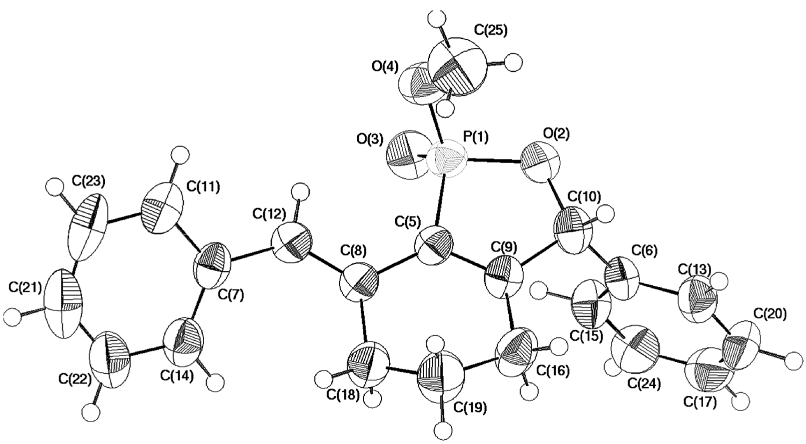
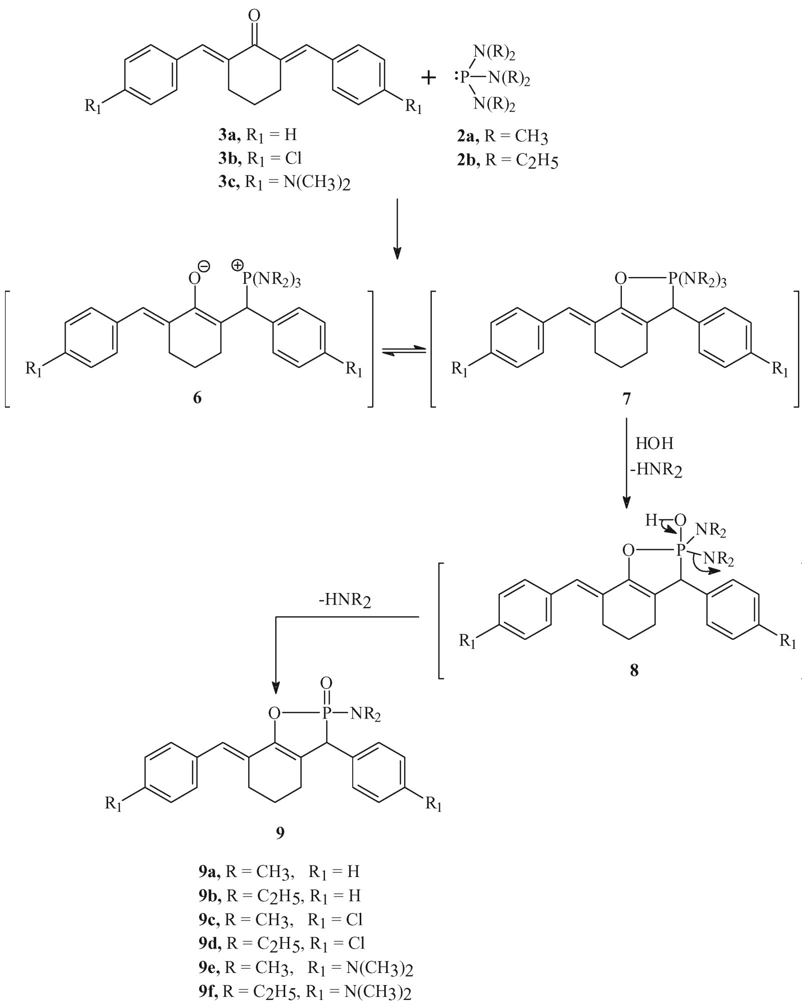


FIGURE 1 Molecular structure of **5a** with the atomic numbering scheme; anisotropic displacement parameters are drawn at the 30% level, and the hydrogen atoms are shown as spheres of arbitrary radii.

Furthermore, this study was extended to include the behavior of 2,6-bis(benzylidene) cyclohexanones (**3a–3c**) toward tris(dialkylamino)phosphines **2a–2b** to determine the preferential site of attack. We have found that 2,6-dibenzylidene cyclohexanone **3a** reacts with tris(dimethylamino)phosphine **2a** in refluxing toluene to give (7-benzylidene-2-oxo-3-phenyl-2,3,4,5,6,7-hexahydro-$2\lambda^5$-benzo[d][1,2]oxaphosphol-2-yl)-dimethylamine (**9a**) (Scheme 3). The assigned oxaphosphole structure **9a** was based on the following



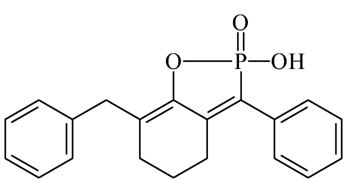
SCHEME 3

evidence: The IR spectrum of **9a** exhibits intense bands at 1240 (P=O), 1320 cm^{-1} and 860 cm^{-1} due to the absorption of the P-N $(CH_3)_2$.[11] The ^1H NMR spectrum (in d_6-DMSO) of **9a** showed a doublet centered at $\delta = 2.68$ ($J_{HP} = 10.20$ Hz) due to the 6H of the dimethylamino group, a doublet centered at 4.26 ppm with $^2J_{HP} = 18.75$ Hz due to the methine proton attached to the phosphorus. The aromatic protons appeared as multiplet at 7.40–7.48 (10H, Ar). The spectrum of **9a** exhibits triplet at 1.69 (t, 2H, CH_2), 2.01 (t, 2H, CH_2), multiplet at 1.94 (m, 2H, CH_2) and singlet at 6.73 (s, 1H, =CH). The ^{31}P NMR gave one signal at $\delta = 46.02$, which confirms the cyclic oxaphosphole structure.[16]

The ^{13}C NMR spectrum of **9a** adds good support for the proposed structure, which reveals the methine proton attached to the phosphorus as doublet at 45.86 with $J_{CP} = 107.2$ Hz (cf. the Experimental section). Moreover, elemental analysis and molecular weight determination (MS) of **9a** support the molecular formula. Similarly, compound **3a** reacts with tris(diethylamino)phosphine **2b** to give colorless crystalline compound formulated as **9b** (Scheme 3, Experimental). Moreover, the reaction of tris(dialkylamino)phosphines **2a** and **2b** with **3b** and **3c**, in dry toluene, proceeds at reflux temperature to give pure adducts formulated as **9c**, **9d**, **9e**, **9f**, respectively (Scheme 3).

Structural elucidation of **9c–9f** is based on elemental analysis, IR, ^1H, ^{13}C, ^{31}P NMR, and mass spectroscopic data (cf. the Experimental section). We propose the reaction course depicted in Scheme 3. Thus, a nucleophilic attack of the phosphite-phosphorus on the most reactive center of **3** leads to the dipolar adduct **6**, which undergoes ring closure giving structure **7**. The latter, due to its structural features, could collapse to the most stable form **9** through the rapid hydrolysis of **7** (by the presence of unavoidable moisture) to give intermediate **8**, which undergoes further decomposition yielding **9**.[17]

It is worthy to note that when compound **9a** was boiled for 1 h in xylene, the new 7-benzyl-3-phenyl-2,4,5,6-tetrahydro-1,2-benzoxaphosphol-2-ol-2-oxide **10** was obtained in 95% yield.



10

Product **10** is pure and possesses a sharp melting point. The structure of **10** was assigned based on the X-ray analysis together with microanalysis, IR, ^1H NMR, and mass spectral data (cf. the Experimental

TABLE II Selected Bond Lengths (Å) and Angles (°)

Compound **5a**	Compound **10**
P1-O2 1.593(14) P1-C15 1.779 (2)	P1-O2 1.517(2) P1-C7 1.776(3)
O2-C10 1.453 (2) C9-C10 1.522(3)	O4-C6 1.412(3) C6-C12 1.455(3)
C5-C9 1.335(3) P1-O3 1.454(14)	C12-C7 1.357(3) P1-O3 1.501(2)
P1-O4 1.566 (2) O4-C25 1.424(3)	P1-O4 1.600(2) C11-C13 1.500(4)
C5-C8 1.474 (2) C5-C9 1.335(3)	C12-C15 1.501(4) C5-C7 1.471(4)
C7-C12 1.469(3) C21-C22 1.358(4)	C5-C21 1.390(4) C13-C14 1.511(4)
O2-P1-O3 115.56(8)	P1-O4-C6 111.9(2)
O2-P1-O4 106.62(8)	O4-C6-C12 110.7(2)
O2-P1-C5 95.34(8)	P1-C7-C12 106.7(2)
P1-C5-C9 108.87(13)	O3-P1-O4 109(11)
O4-P1-C5 111.95(8)	O2-P1-O3 112.6(10)

X-Ray Crystallographic Study:[12–13] The crystal structure was solved and refined, using maXus (Nonius, Delft and Mac Science, Japan). MoK_{α} ($\lambda = 0.71073$ Å) and a graphite monochromator were used for data collection. A summary of the crystal analysis parameters is given in Table I. CCDC (699015, **5a**; 699016, 10) contains the supplementary crystallographic data for this article.

These data can be obtained from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

section). In order to unambiguously identify the structure of the reaction product **10**, an X-ray structure determination was performed (Figure 2, Tables I and II).

From the results of the present investigation, it could be concluded that the reaction of 2,6-bis(benzylidene)cyclohexanones **3a–3c** with dialkylphosphonates **1a–1b** proceeds in a different manner

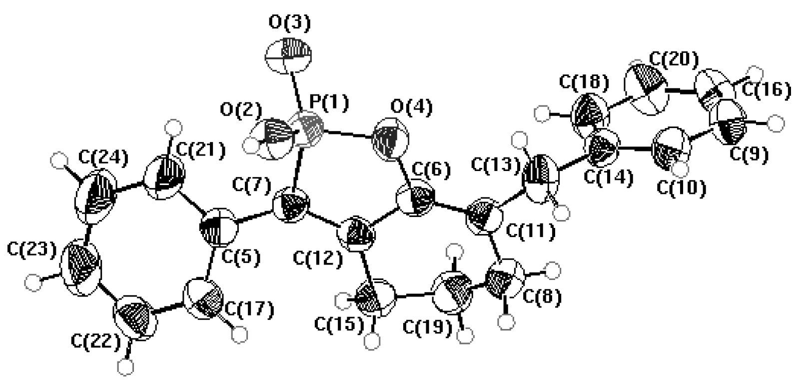


FIGURE 2 Molecular structure of **10** with atomic numbering scheme; anisotropic displacement parameters are drawn at the 30% level, and the hydrogen atoms are shown as spheres of arbitrary radii.

from that with tris(dialkylamino)phosphines **2a–2b**. Formation of (7)-1-alkoxy-3-phenyl-7-(phenylmethyliden)-1,3,4,5,6,7-hexahydro-2,1-benzoxaphosphole-1-oxide **5a–5d** seems to proceed via a neucleophilic attack of phosphonates **1** on the carbonyl functionality in **3**, while tris(dialkylamino)phosphines **2a–2b** react with **3a–3c**, through addition to the β-carbon atom of α,β-unsaturated ketone system, to give hexahydro-1,2-benzoxaphosphole-2-oxide adducts **9a–9f**. These findings supplement the wide aspect for utilization of dialkylphosphonates and tris(dialkylamino)phosphines in the synthesis of new benzoxaphosphole derivatives.

EXPERIMENTAL

All melting points are uncorrected. The IR spectra were measured in KBr pellets with a Perkin-Elmer Infrared Spectrophotometer Model 157 (Grating). The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ and d_6-DMSO as solvents on a JEOL-300 MHz Spectrometer, and the chemical shifts were recorded in δ values relative to TMS. The ^{31}P NMR spectra were taken with a Varian CFT-20 (vs. external 85% H_3PO_4 standard). The mass spectra were performed at 70 eV on a Shimadzu GCS-OP 1000 Ex Spectrometer. Elemental analyses were performed using the Elementer Varu El Germany Instrument.

Reaction of Dialkylphosphonate 1a–1b with 2,6-Bis(benzylidene)cyclohexanone (3a)

Dialkylphosphonate **1a** or **1b** (0.002 mol) was added dropwise to a solution of compound **3a** (0.27 g, 0.001 mol) in dry toluene (30 mL), and the reaction mixture was refluxed for 10 h. After evaporation of the volatile materials under reduced pressure, the residue was applied to silica gel column chromatography. The eluent, yield, and mp are given below for adducts **5a** and **5b**.

(7)-1-Methoxy-3-phenyl-7-(phenylmethylidene)-2,3,4,5,6,7-hexahydro-2,1-benzoxaphosphole-1-oxide (5a)

Eluent**:** acetone:petroleum ether (30:70, v/v), colorless crystals, mp 186–187 °C, yield 85%. Anal. calcd $C_{21}H_{21}O_3P$(352.37): C, 71.58, H, 6.00, P, 8.77. Found: C, 71.73, H, 6.16, P, 8.86%. IR (KBr): $\nu = 1240$ (P=O) cm^{-1}, 1040 (POMe) cm^{-1}; ^{1}H NMR ($CDCl_3$) $\delta = 3.86$ (d, 3H, P-OCH_3, $^{3}J_{HP} = 11.87$ Hz), 2.16 (t, 2H, CH_2), 1.88 (t, 2H, CH_2), 1.72 (m, 2H, CH_2), 5. 64 (d, 1H, P-O-CH, $^{3}J_{HP} = 5.8$ Hz), 6.70 (s, 1H, =CH); 7.26–7.39 (m, 10H, Ar) ppm. ^{31}P NMR: $\delta = 37.62$ ppm MS m/z (%):352 (M^{+}, 100).

(7)-1-Ethoxy-3-phenyl-7-(phenylmethyliden)-2,3,4,5,6,7-hexahydro-2,1-benzoxaphosphole-1-oxide (5b)

Eluent**:** ethyl acetate:petroleum ether (70:30, v/v), colorless crystals, mp 258–260°C, yield 78%. Anal.calcd $C_{22}H_{23}O_3P$ (366.39): C, 72.12, H, 6.33, P, 8.45 Found: C, 72.17, H, 6.39, P, 8.53%. IR (KBr): $\nu' = 1243$ (P=O) cm^{-1}, 1045 (POEt) cm^{-1}; ^1H NMR (300 MHz,$CDCl_3$): $\delta = 1.15$ [t, 3H, P (OCH_2CH_3)], 4.02 [q, 2H, $^3J_{HP} = 11.5$ Hz, P(OCH_2CH_3)],1.55, 1.37, 2.24 ($3CH_2$), 5.62 (d, $^3J_{HP} = 5.4$Hz,P-O-CH), 6.63 (s, 1H, =CH), 7.11–7.44 (m, 10H, Ar) ppm; ^{13}C NMR (300 MHz,$CDCl_3$): $\delta = 118.67$ (C-P, $^1J_{CP} = 70.50$ Hz), 87.8 (P-O-CH), 26.6, 30.4, 23.7 ($3CH_2$, cyclohexanone), 140.6 (C = C-P), 129.8, 130.5, 128.8, 131 (C_6H_5), 130.5, 128.8, 127.8, 126.3 (C_6H_5) ppm. MS: m/z (%): 366 (M^+,100)

Reaction of Dialkylphosphonate 1a and/or 1b with 2,6-Bis(4-chlorobenzylidene)-cyclohexanone (3b)

A mixture of 0.002 mol dialkylphosphonate **1a** or **1b** and 0.001 mol of **3b** in dry toluene (30 mL) was refluxed for 18–20 h. The volatile materials were evaporated under reduced pressure. The residue was subjected to silica gel column chromatography to give the products.

(7)-3-(4-Chlorophenyl)-7-[(4-chlorophenyl)-methylidene]-1-methoxy-1,3,4,5,6,7-hexahydro-2,1-benzoxaphosphole-1-oxide (5c)

Eluent**:** Acetone:petroleum ether (25:75, v/v), colorless crystals, mp 187–188 °C, yield 80%. Anal calcd. for $C_{21}H_{19}Cl_2O_3P$ (421.25) C, 59.87, H, 4.55, Cl, 16.83, P, 7.35, Found. C, 59.95, H, 4.59, Cl, 16.89, P, 7.40. IR (KBr): $\nu = 1040$ ($POCH_3$), 1250 (P=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 3.56$ (d, 3H, P-OCH_3, $^3J_{HP} = 11.87$ Hz), 2.45 (t, 2H, CH_2), 1.97 (t, 2H, CH_2), 1.77 (m, 2H, CH_2), 5.68 (d, 1H, P-O-CH, $^3J_{HP} = 5.40$ Hz), 6.78 (s, 1H, =CH), 7.50–7.29 (m, 8H, Ar) ppm; ^{13}C NMR (300 MHz, $CDCl_3$): $\delta = 117.9$ (C-P, $^1J_{CP} = 75$ Hz), 53.5 (P-OCH_3), 87.3 (P-O-CH, $^2J = 27$ Hz), 26.6, 30.4, 23.7 ($3CH_2$, cyclohexanone), 140.6 (C = C-P), 135.8, 130.5, 128.8, 131.3 (4-Cl-C_6H_4), 133.5, 128.8, 127.8, 133.3 (4-Cl-C_6H_4) ppm. MS: m/z (%): 421 (M^+,70).

(7)-3-(4-Chlorophenyl)-7-[(4-chlorophenyl)-methylidene]-1-ethoxy-1,3,4,5,6,7-hexahydro-2,1-benzoxaphosphole-1-oxide (5d)

Eluent**:** ethyl acetate:petroleum ether (15:85, v/v), colorless crystals, mp 203–205 °C, yield 90%. Anal. calcd for $C_{22}H_{21}Cl_2O_3P$ (435.28): C, 60.70, H, 4.86, Cl, 16.29, P, 7.12. Found. C, 60.76, H, 4.88, Cl, 16.34, P, 7.17%. IR (KBr): $\nu = 1242$ (P=O), 1042 (POEt) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.39$ [t, 6H, P(OCH_2CH_3)$_2$], 4.23 [m, 4H, $J_{HP} = 7.4$

Hz, $P(OCH_2CH_3)_2$], 2.15, 1.90 (t, 4H, $2CH_2$), 1.7 (m, CH_2,2H), 5.63 (d, P-O-CH, $^3J_{HP} = 6.20$ Hz), 6.86 (s, =CH), 7.25–7.35 (m, 8H, Ar) ppm. ^{31}P NMR: $\delta = +\ 37.62$ ppm. MS: m/z (%): 435 (M^+, 85).

Reaction of 3a with Tris(dialkylamino)phosphine 2a or 2b

A mixture of **3a** (0.27 g; 0.001 mol), tris(dialkylamino)phosphine **2a** or **2b** (0.002 mol) and dry toluene (30 mL) was refluxed until no more of the starting materials could be detected (TLC, 6–8 h). The reaction mixture was evaporated under reduced pressure and then applied to silica gel column chromatography to give products **9a** and **9b**.

[7-(Benzylidene)-2-oxo-3-phenyl-2,3,4,5,6,7-hexahydro-2λ⁵-benzo[d][1,2]oxa-phosphol-2-yl]-dimethylamine (9a)

Eluent**:** ethyl acetate:petroleum ether (90:10, v/v), colorless crystals, mp 160–161 °C, yield 85%. Anal. calcd. for $C_{22}H_{24}NO_2P$ (365.41): C, 72.31, H, 6.62, N, 3.83, P, 8.48. Found. C, 72.38, H, 7.67, N, 3.88, P, 8.50%. IR (KBr): $\nu = 1240$ (P=O) cm^{-1}, 1320 cm^{-1}, 860 cm^{-1} (P-N$(CH_3)_2$; ^{1}H NMR (DMSO) :$\delta = 2.68$ (d, $J_{HP} = 7.5$ Hz, 6H, P-N$(CH_3)_2$), 1.94 (m, 2H, CH_2), 1.69 (t, 2H, CH_2), 2.01 (t, 2H, CH_2), 4.26 (d, $^2J_{HP} = 18.75$ Hz, P-CH), 7.17–7.40 (m, 10H, Ar), 6.73 (s, -CH =) ppm; ^{13}C NMR (DMSO): $\delta = 45.89$ (P-CH, $^1J_{CP} = 107.2$ Hz), 38.5 [P-N$(CH_3)_2$] ppm; ^{31}P NMR (DMSO):$\delta = +46.02$ ppm; MS, m/z (%): 365 (M^+,100).

[7-(Benzylidene)-2-oxo-3 -phenyl)-2,3,4,5,6,7-hexahydro-2λ⁵-benzo[d][1,2]oxaphosphol-2-yl]-diethylamine (9b)

Eluent**:** ethyl acetate:petroleum ether (10:90, v/v), colorless crystals, mp 181–182 °C, yield 80%. Anal.calcd. for $C_{24}H_{28}NO_2P$(393.46): C, 73.26, H, 7.17, N, 3.56, P, 7.87. Found. C, 73.29, H, 7.20, N, 3.58, P, 7.89%. IR (KBr): $\nu = 1325$, 865 (P-N-CH_2CH_3), 1242 (P=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.87$ (d, $^2J_{HP} = 13.5$ Hz, P-CH), 3.22, 3.15 [q, 4H, N$(CH_2CH_3)_2$], 1.15 [t, 6H, N$(CH_2CH_3)_2$], 2.06 (t, 2H, CH_2), 1.62 (t, 2H, CH_2), 1.77 (m, 2H, CH_2), 6.89 (s, 1H, HC =), 7.27- 7.36 (m,10H, Ar) ppm; ^{13}C NMR (300 MHz, $CDCl_3$): $\delta = 45.1$ (d, P-CH, $^1J_{CP} = 105.8$ Hz), 40.6 [P-N$(CH_2CH_3)_2$], 14.8 [P-N$(CH_2CH_3)_2$] ppm. MS: m/z (%): 393 (M^+, 100).

Reaction of Trisdialkylaminophosphine 2a and 2b with 2,6-Bis(4-chlorobenzylidene)-cyclohexanone (3b)

To a solution of **3b** (0.34 g; 0.001 mol) in dry toluene (30 mL), tris(dialkylamino)phosphine **2a** or **2b** (0.002 mol) was added dropwise, and the reaction mixture was refluxed for 8–10 h. The solution was evaporated under reduced pressure, and the residue was subjected to silica gel column chromatography to give **9c** and **9d**.

[7-(4-Chlorobenzylidene)-3-(4-chlorophenyl)-2-oxo-2,3,4,5,6,7-hexahydro-2λ⁵-benzo-[d][1,2]oxaphosphol-2-yl]-dimethylamine (9c)

Eluent**:** ethyl acetate:petroleum ether (95:5, v/v), colorless crystals, mp 245–247°C, yield 75%. Anal. calcd. for $C_{22}H_{22}$ Cl_2NO_2P (434.30) C, 60.84, H, 15.11, Cl, 16.33, N, 3.23, P, 7.13. Found. C, 60.88, H, 15.17, Cl, 16.38, N, 3.25, P, 7.17%. IR (KBr): ν = 1312,865 cm^{-1} P [N(Me)$_2$]; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.53 (d, $^2J_{HP}$ = 13.6 Hz, P-CH), 2.47 (d, $^3J_{HP}$ = 9.3 Hz, 6H, P-N(CH_3)$_2$), 1.96 (t, 2CH_2), 1.37 (m, CH_2), 6.36 (s, CH, 1H), 7.15–7.24 (m, 8H, 4-Cl-Ar) ppm;^{13}C NMR (300 MHz, $CDCl_3$): δ = 45.5 (C-P, d, $^1J_{CP}$ = 104.9 Hz), 123.9, 140.6 (C_6H_4-CH = C),121.30, 140.22 (C=C), 130.5, 128.8, 131.2, 135.9, 127.8,126.4, 125.8, 131.2 (2C_6H_4) ppm. MS, m/z (%): 434 (90, M^+).

[7-(4-Chloro-benzylidene)-3-(4-chlorophenyl)-2-oxo-2,3,4,5,6,7-hexahydro-2λ⁵-benzo-[d][1,2]oxaphosphol-2-yl]-diethylamine (9d)

Eluent**:** acetone:petroleum ether (15:85, v/v), colorless crystals, mp 194–195 °C, yield 85%. Anal. calcd for. $C_{24}H_{26}Cl_2N$ O_2P (462.35)C, 62.35, H, 5.67, Cl, 15.34, N, 3.03, P, 6.70. Found. C, 62.38, H, 5.70, Cl, 15.37, N, 3.07, P, 6.73%. IR (KBr): ν = 1310, 854 [P-N(CH_2CH_3)$_2$] cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) : δ = 3.79 (d, $^2J_{HP}$ = 13.2 Hz, P-CH), 3.23, 3.14 [q, 4H, N(CH_2CH_3)$_2$], 1.2 [t, 6H, N(CH_2CH_3)$_2$], 2.01 (t, 2H, CH_2), 1.77 (m, 2H, CH_2), 1.58 (t, 2H, CH_2), 6.82 (s, 1H, -CH =), 7.13–7.34 (m, 8H, Ar) ppm; ^{13}C NMR (300 MHz, $CDCl_3$) : δ = 47.14 (d, P-CH, J_{CP} = 104.0 Hz), 38.97, 38.94 (2NCH_2 CH_3), 14.55 (2NCH_2CH_3), 26.71, 23.88, 22.73 (3CH_2), 135.2, 130.5, 130.4, 128.8 (4-Cl-C_6H_4), 132.6, 133.0, 128.9, 128.63 (4-Cl-C_6H_4), 123.5, 148.4 (C =CH-), 148.4 (C-O^-) ppm. MS: m/z (%): 462 ($M^{+,}$ 85).

Reaction of 2,6-Bis(4-dimethylaminobenzylidene) cyclohexanone (3c) with Tris(dialkylamino)phosphine 2a and 2b

Tris(dialkylamino)phosphine **2a** or **2b** (0.002 mol) was added dropwise to a solution of compound **3c** (0.36 g; 0.001 mol) in dry toluene (30 mL), and the reaction mixture was refluxed for 12–15 h. After evaporation of the volatile materials under reduced pressure, the residue was applied to silica gel column chromatography. The eluent, yield, and mp are given below for adducts **9e** and **9f**.

[7-(4-Dimethylaminobenzylidene)-3-(4-dimethylaminophenyl)-2-oxo-2,3,4,5,6,7-hexahydro-2λ⁵-benzo[d][1,2]oxaphosphol-2-yl]dimethylamine (9e)

Eluent: ethyl acetate:petroleum ether (12:88, v/v), yellow crystals, mp 226–228 °C, yield 80%. Anal. calcd. for $C_{26}H_{34}N_3O_2P$ (451.54) C, 69.16, H, 7.59, N, 9.31, P, 6.86. Found. C, 69.28, H, 7.64, N, 9.35, P, 6.88%. IR (KBr): ν = 1240 (P=O) cm^{-1}, 1320, 860 ($PN(CH_3)_2$) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) : δ = 2.79 (d, 6H, $^3J_{HP}$ = 9.9 Hz, $P(N\text{-}CH_3)_2$), 2.98, 2.96 (12H, 2 ($N(CH_3)_2$), 3.78 (d, 1H, $^2J_{HP}$ = 13.2 Hz, P-CH), 6.70–7.27 (m, 9H, Ar-H, and =CH) ppm; ^{13}C NMR (300 MHz,$CDCl_3$): δ = 45.86 (HC-P, d, $^1J_{CP}$ = 107.2 Hz), 40.1 [$N(CH_3)_2$], 38.1{d, $^2J_{CP}$ = 6.2 Hz, P[N $(CH_3)_2$]}, 148.60 [d, $^2J_{CP}$ = 9.7 Hz, P[O-C=C], 129.70 [d, $^2J_{CP}$ = 5.96 Hz, Ar-C-CH-P] ppm; ^{31}P NMR: δ = +46.02 ppm. MS, m/z (%): 451 (M^+,100).

[7-(4-Dimethylaminobenzylidene)-3-(4-dimethylaminophenyl)-2-oxo-2,3,4,5,6,7-hexahydro-2λ⁵-benzo[d][1,2]oxaphosphol-2-yl]-diethylamine (9f)

Eluent: ethyl acetate:petroleum ether (18:82, v/v), colorless crystals, mp 246–247°C, yield 85%. Anal. calcd. for $C_{28}H_{38}N_3O_2P$ (479.59): C, 71.32, H, 6.41, N, 8.91, P, 6.57. Found. C, 71.35, H, 6.43, N, 8.94, P, 6.59%. IR (KBr): ν = 1356, 898 ($P\text{-}N(Et)_2$) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) : δ = 1.21 (t, 6H, $2NCH_2CH_3$), 3.81 (d, $^2J_{HP}$ = 10.8 Hz, P-CH), 3.00, 2.95 [12H, $2N(CH_3)_2$], 3.16, 3.09 (m, 4H, $2NCH_2CH_3$), 1.77 (m, 4H, $2CH_2$), 2.06 (t, 2H, CH_2), 6.73–7.31 (m, 9H, Ar, and =CH) ppm; ^{13}C NMR (300 MHz, $CDCl_3$): δ = 46.7 (HC-P, $^1J_{CP}$ = 107.5 Hz), 38.78, 38.75 [$P\text{-}NCH_2CH_3$,$^3J_{CP}$ = 4.8 Hz), 14.5 ($P\text{-}NCH_2CH_3$), 26.97, 23.92, 22.96 ($3CH_2$), 40.7 [$P\text{-}N(CH_3)_2$], 121.4, 148.5 (C =CHAr), 148.6 (C-O), 130.3, 129.8, 125.3, 124.4 (CH-Ar), 129.7, 124.5, 124.1, 116.4 (Ar-CH =) ppm. MS, m/z (%): 479 (100) [M^+].

7-Benzyl-3-phenyl-2,4,5,6-tetrahydro-1,2-benzoxaphosphol-2-ol-2-oxide (10)

0.36 g (0.001 mol) of **9a** was refluxed in dry xylene for 1 h. After evaporation of the volatile materials under reduced pressure, the residue was crystallized from toluene to give **10** as colorless crystals, mp 134–135 °C. Anal. calcd.for $C_{20}H_{19}O_3P$ (338.34): C, 71.00, H, 5.66, P, 9.15. Found. C, 71.05, H, 5.69, P, 9.20%. IR (KBr): ν = 2560 (P-OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 3.6 (s, 2H, CH_2-benzyl), 2.17, 2.18, (2t, 4H, $2CH_2$), 2.70 (m, 2H, CH_2), 7.22–7.55 (m, 10H, Ar), 1.7 (b, OH, exchangeable with D_2O) ppm. MS, m/z (%): 338 (M^+,100).

TABLE III The Antibacterial and Antifungal Activities of the Synthesized Compounds

	Inhibition zone diameter mm/mg sample	
	Gram-negative bacteria	Gram-positive bacteria
Compound No.	*Escherichia coli*	*Staphylococcus aureus*
Chloroform	0.0	0.0
3b	11	12
3c	12	12
9e	12	13
5d	14	15
9f	11	12
5c	1.0	3.0
9a	0.6	2.6
5a	0.4	1.1

BIOLOGICAL ACTIVITY

The antibacterial and antifungal activities were carried out in the Microbiology Division of the Microanalytical Center of Cairo University, using the diffusion plate method.[18–21] A bottomless cylinder containing a measured quantity (1 mL, mg/mL) of the sample is placed on a plate (9 cm diameter) containing a solid bacterial medium (nutrient agar broth) or a fungal medium (Dox's medium), which has been seeded with the spore suspension of the test organism. After incubation (24 h for bacteria and 5 days for fungi), the diameter of the clear zone of inhibition surrounding the sample is taken as a measure of the inhibitory power of the sample against the particular test organism (1% inhibition = sample inhibition zone (cm)/plate diameter $\times$ 100). All measurements were done in chloroform as the solvent, which has zero inhibition activity. The antimicrobial activity of the tested compounds was examined with Gram-positive bacteria *Staphylococcus aureus* and Gram-negative bacteria *Escherichia coli*. As shown in (Table III), the cyclic adduct **5** was found be active against Gram-negative bacteria *Escherichia coli* with respect to other derivatives. The antifungal activity of compounds **4a** and **5** was found to be higher than others.

REFERENCES

[1] J. R Dimmock and M. L Wong, *Can. J. Pharm. Sci.*, **11,** 35 (1976).

[2] L. S. Boulos and H. A. Abd El-Malek, *Phosphorus, Sulfur, and Silicon*, **179,** 97 (2004).

[3] L. S. Boulos and H. A. Abd El-Malek, *Indian J. Heterocycl. Chem.*, **14,** 245 (2005).
[4] L. S. Boulos, N. K. El-Din, and M. H. N. Arsanious, *Phosphorus, Sulfur, and Silicon*, **181,** 1467 (2006).
[5] L. S. Boulos, E. M. A Yakout, and M. H. N. Arsanious, *Phosphorus, Sulfur, and Silicon*, **181,** 1615 (2006).
[6] M. H. N. Arsanious and L. S. Boulos, *Monatsh. Chem.*, **137,** 1177 (2006).
[7] L. S. Boulos, M. H. N. Arsanious, and E. M. A Yakout, *Monatsh. Chem.*, **138,** 979 (2007).
[8] L. S. Boulos and M. H. N. Arsanious, *Synth. Commun.*, **32,** 2779 (2001).
[9] M. H. N. Arsanious and L. S. Boulos, *Heteroatom. Chem.*, **12,** 511 (2001).
[10] M. Hesse, M. Meier, and B. Zeeh, *Spektroskopische Methoden in der Organischem Chemie* (Thieme Verlag, Stuttgart, Germany, 1991), Chap. 2.1, p. 64.
[11] E. Pretsch, J. Seibl, and W. Simon, *Tables of Spectral Data for Structure Determination of Organic Compounds* (Springer-Verlag, Berlin, Germany, 1983).
[12] S. Mackay, C. J Gilmore, C. Edward, N. Stewart, and K. Shankland, Maxus Computer Program for the Solution and Refinement of Crystal Structures Bruker Nonius, The Netherlands, MacSciene, Japan, and The University of Glasgow (1999).
[13] C. K. Johnson, ORTEP-11: A Fortran Thermal-Ellipsoid Plot Program. Report ORNL-5138, Oak Ridge, Tennessee, USA (1976).
[14] W. Z. Otwinowski, In *Methods in Enzymology*, C. W. Minor, Jr. and R. M. Carter Sweet, Eds. (Academic Press, New York, 1997), p. 276.
[15] A. Altomare, G. Cascarano, C. Giacovazzo, M. C. Guagliavdi Burla, G. Polidori, and M. Camalli, *J. Appl. Cryst.* **27,** 435 (1994).
[16] M. M. Crutchfield, C. H. Dungan, J. H. Letcher, V. Mark, and J. R. Van Wazer, *Topics in Phosphorus Chemistry*, M. Graysor and E. J. Griffith, Eds. (Interscience Publishers, New York, 1967), vol. 5, p. 227.
[17] A. A. El-Kateb, L. S. Boulos, and H. A. Abd El-Malek, *Phosphorus, Sulfur, and Silicon*, **83,** 105 (1993).
[18] S. Apers, D. Paper, J. Burgermeister, S. Baronikova, S. Van Dyck, G. Lemiere, A. Vlietinck, and L. Pieters, *J. Nat. Prod.*, **65,** 718 (2002).
[19] J. A. Walker, K. Rossen, R. A. Reamer, R. P. Volante, and P. T. Reider, *Tetrahedron Lett.*, **40,** 4917 (1999).
[20] A. G. Gamzalez, J. B Barrera, A. C. Yames, J. G. Diaz, and E. M. Rodriguez, *Phytochemistry*, **28,** 2520 (1989).
[21] C. F. Carvalho and M. V. Sargent, *J. Chem. Soc., Perkin Trans. 1*, 1605 (1984).