



Faculty of Science
Chemistry Department

**Synthesis of New Organophosphorus Compounds of
Anticipated Biological Activity by The Reaction of
Some Phosphorus Reagents with Active Centers in
Some Organic Compounds**

A DISSERTATION

Presented By

Ewies F. E. Mahmoud

B.Sc., M. Sc. (Cairo University)

National Research Centre

For

The Degree of Doctor Philosophy of Science

(In Organic Chemistry)

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Ain Shams University

Cairo, Egypt

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APPROVAL SHEET OF THE THESIS

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Synthesis of New Organophosphorus Compounds of Anticipated Biological Activity by The Reaction of Some Phosphorus Reagents with Active Centers in Some Organic Compounds

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Ewies F. Ewies

Cairo 2012

TO

MY WIFE AZZA

WHO ENCOURAGE ME

TO PROCEED

AT EACH & EVERY STEP

ABSTRACT

Name: Ewies Fawzy Ewies Mahmoud

Title: Synthesis of New Organophosphorus Compounds of Anticipated Biological Activity by The reaction of Some Phosphorus Reagents with Active Centers in Some Organic Compounds

Degree: Ph.D.

The thesis included three parts.

In the first part: the study has been focused on the synthesis of new bisphosphonate and bisphosphonic acid oxazolone derivatives with anticancer and *N*-(1-dialkylcarbamoyl)-2-phenylvinylbenzamides derivatives with antischistosomal activity. The reaction of 5(4*H*)-oxazolones with tetraethyl methanediylbis (phosphonate) afforded the new 1,1-bisphosphonate and 1,1-bisphosphonic acid derivatives. Moreover, 5(4*H*)-oxazolones reacted with *Wittig* reagents to give the corresponding heterocyclic products. Treatment of 5(4*H*)-oxazolones with trisdialkylaminophosphanes gave the corresponding *N*-(1-dialkylcarbamoyl)-2-phenylvinylbenzamides.

The second part has been extended to focus on uses of pyrazoles in synthesis of some new triphenylphosphanylidenes, alkylphosphonates and their antimicrobial activity. The reaction of 5(4*H*)-pyrazolone with phosphorus ylides afforded the new triphenylphosphanylidene alkanone derivatives. Moreover, its benzylidene reacted with *Wittig-Horner* reagents to give the corresponding dialkoxyphosphoryl, alkylphosphonate and heterocyclic products. Treatment of pyrazole-4-carbaldehyde with *Wittig-Horner* reagent and trialkyl phosphites gave the respective alkyl phosphonate adducts.

In the third part, the study has been focused uses of quinones in synthesis of new 1,2-bis(diphenylphosphino)alkanes derivatives *via* redox reaction. The reaction of 1,2-bis(diphenylphosphino)ethane with substituted *o*-benzoquinones afforded the new bis(6-hydroxycyclohexa-2,4-dienone) derivatives. Treatment of the same reagent with *o*-naphthoquinone, phenanthrenequinone and acenaphthenequinone gave the respective bis(diphenylphosphoryl)ethylidenes or diacenaphthylenone derivatives. On the other hand, *p*-quinones react with 1,2-bis(diphenylphosphino)methane to yield the corresponding 4-hydroxycyclohexa-2,5-dien-1-ones.

Mechanisms accounting for the formation of the new products are discussed. The biological activity of the newly synthesized compounds was also examined.

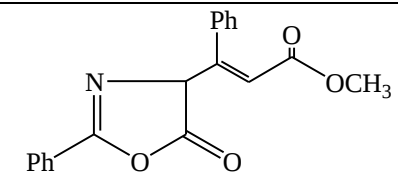
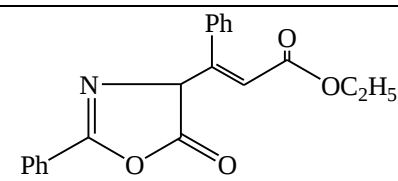
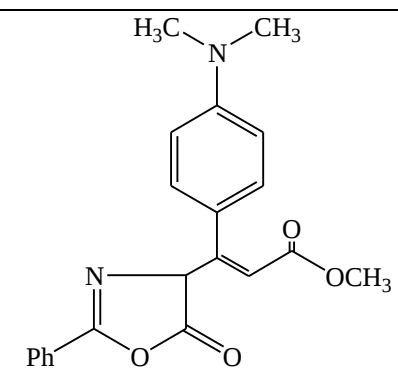
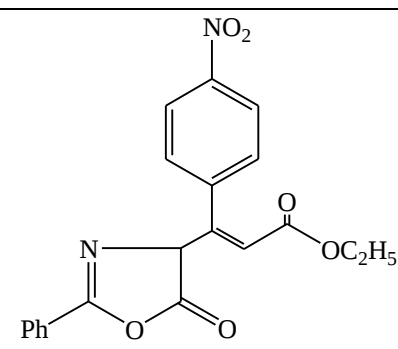
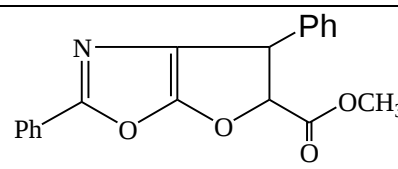
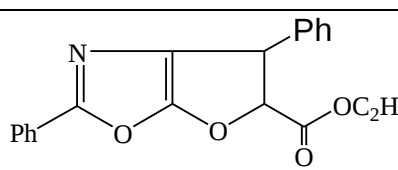
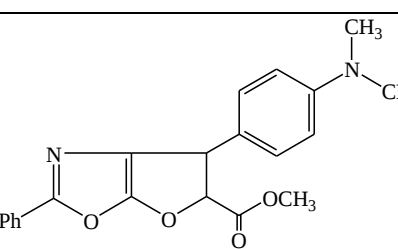
Keywords: *Wittig* Reagents, *Wittig-Horner* Reagents, Trialkyl Phosphites, Oxazolones, Pyrazoles, *o*-Quinones, *p*-Quinones, 1,1-Bisphosphonate, 1,1-Bisphosphonic Acid, Triphenylphosphanylidenes, 1,2-Bis(diphenylphosphino)alkanes, Anticancer Activity, Antischistosomal Activity, Antimicrobial Activity.

List of Abbreviations

^{13}C NMR	Carbon Nuclear Magnetic Resonance
^1H NMR	Proton Nuclear Magnetic Resonance
^{31}P NMR	Phosphorus Nuclear Magnetic Resonance
b.r.	Boiling range
DDQ	Dicyanochloroquinone
DECP	Diethylcyanophosphonate
DMSO	Dimethylsulfoxide
Fig	Figure
g	Gram
h	Hour
Hz	Hertz
IC ₅₀	Inhibitory concentration
IR	Infrared
LDA	Lithium diisopropylamine
m.p.	Melting point
mg	Milligram
min	Minute
mL	Milliliter
mmoles	Millimoles
MS	Mass Spectroscopy
MTT	(3-[4,5-dimethylthiazole-2-yl]-2,5-diphenyltetrazolium bromide)
ppm	Part Per Million
r.t.	Room temperature
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TPP	Triphenylphosphane
TPPO	Triphenylphosphane Oxide
WH	<i>Wittig-Horner</i> Reagent
WHE	<i>Wittig-Wadsworth-Emmons</i>

LIST OF NEW SYNTHESIZED COMPOUNDS

Compounds	Structure
Tetraethyl [2-(5-oxo-2-phenyl-4,5-dihydro-1,3-oxazol-4-yl)-2-phenylethane-1,1-diyl]bisphosphonate 5a	
Diethyl [2-(4,5-dihydro-5-oxo-2-phenyloxazol-4-yl)-2-phenylvinyl] phosphonate 6a	
[2-(5-Oxo-2-phenyl-4,5-dihydro-1,3-oxazol-4-yl)-2-phenylethane-1,1-diyl]bis(phosphonic acid) 7a	
[2-(4-Nitrophenyl)-2-(5-oxo-2-phenyl-4,5-dihydro-1,3-oxazol-4-yl)ethane-1,1-diyl]bis(phosphonic acid) 7b	
2-[(4,5-Dihydro-5-oxo-2-phenyloxazol-4-yl)-2-phenylvinyl] phosphonic acid 8a	
[2-(4-Nitrophenyl)-2-(5-oxo-2-phenyl-4,5-dihydro-1,3-oxazol-4-yl)ethenyl] phosphonic acid 8b	

Methyl 3-(4,5-dihydro-5-oxo-2-phenyloxazol-4-yl)-3-phenylacrylate 9a	
Ethyl 3-(5-oxo-2-phenyl-4,5-dihydro-1,3-oxazol-4-yl)-3-phenylprop-2-enoate 9b	
Methyl 3-[4-(dimethylamino)phenyl]-3-(5-oxo-2-phenyl-4,5-dihydro-1,3-oxazol-4-yl)prop-2-enoate 9c	
Ethyl 3-[3-(4-nitrophenyl)-3-(4,5-dihydro-5-oxo)-2-phenyloxazol-4-yl]acrylate 9d	
Methyl 2,6-diphenyl-5,6-dihydrofuro[3,2-d][1,3]oxazole-5-carboxylate 10a	
Ethyl 2,6-diphenyl-5,6-dihydrofuro[3,2-d][1,3]oxazole-5-carboxylate 10b	
Methyl 6-[4-(dimethylamino)phenyl]-2-phenyl-5,6-dihydrofuro[3,2-d][1,3]oxazole-5-carboxylate 10c	

Ethyl 6-(4-nitrophenyl)-2-phenyl-5,6-dihydrofuro[3,2-d][1,3]oxazole-5-carboxylate 10d	
Methyl (5-oxo-2,7-diphenyl-5H-pyrano[3,2-d][1,3]oxazol-6(7H)-ylidene)ethanoate 11a	
Ethyl (5-oxo-2,7-diphenyl-5H-pyrano[3,2-d][1,3]oxazol-6(7H)-ylidene)ethanoate 11b	
Methyl {7-[4-(dimethylamino)phenyl]-5-oxo-2-phenyl-5H-pyrano[3,2-d][1,3]oxazol-6(7H)-ylidene}ethanoate 11c	
2,4-Diphenyl-5,6-dihydro-4H-cyclopenta[d][1,3]oxazole-5,6-dicarbonitrile 12	
2-[2-Phenyl-4-(3,4,5-trimethoxybenzylidene)-4,5-dihydro-1,3-oxazol-5-yl]but-2-enedinitrile 13	
Methyl [2-phenyl-4-(3,4,5-trimethoxybenzylidene)-1,3-oxazol-5(4H)-ylidene]ethanoate 14	