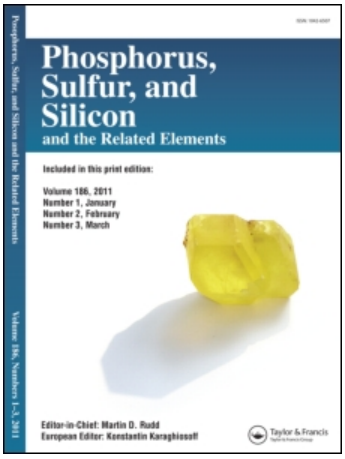


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Novel Organophosphorus Compounds as Potential Antimicrobial Agents

S. R. Lokhandwala[a]; K. R. Desai[a]
[a] Department of Chemistry, Veer Narmad South Gujarat University, Surat, India

To cite this Article Lokhandwala, S. R. and Desai, K. R.(2008) 'Novel Organophosphorus Compounds as Potential Antimicrobial Agents', Phosphorus, Sulfur, and Silicon and the Related Elements, 183: 5, 1264 — 1271
To link to this Article: DOI: 10.1080/10426500701640827
URL: http://dx.doi.org/10.1080/10426500701640827

Phosphorus, Sulfur, and Silicon, 183:1264–1271, 2008

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500701640827

Taylor & Francis
Taylor & Francis Group

Novel Organophosphorus Compounds as Potential Antimicrobial Agents

S. R. Lokhandwala and K. R. Desai
Department of Chemistry, Veer Narmad South Gujarat University, Surat 395 007, India

The 4-Thiazolidinone derivatives of phenophosphazines were synthesized by a reaction of Schiff base derivative of phenophosphazine with Thyoglycollic acid in molar ratio of 1:3 using DMF as solvent. Possible structures have been proposed based on elemental analysis, IR and ^1H NMR spectral studies. The antibacterial and antifungal activities of these derivatives have been evaluated against pathogens E. coli, S. typhi, S. aureus, B. subtilis, A. niger, and C. Albicans.

Keywords Antibacterial activity; Antifungal activity; Phenophosphazine; Thiazolidinone

INTRODUCTION

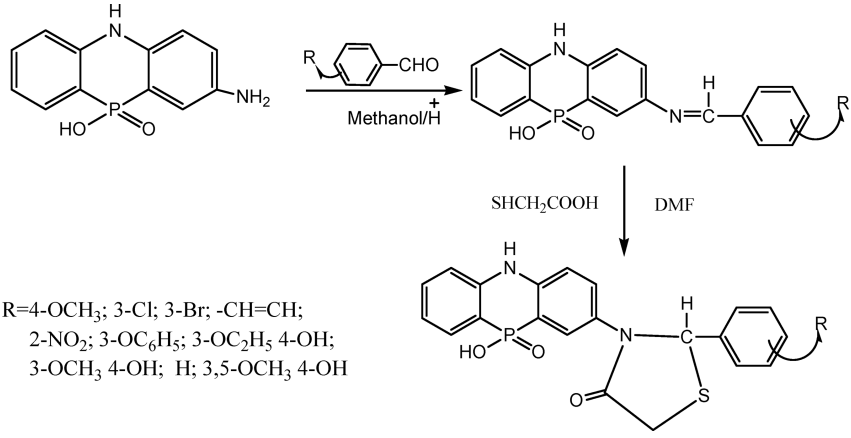
Phosphorus has important and multifaceted functions in the biochemistry of the body. It is ubiquitous in an anatomical term and is of great importance in a host of reactions throughout virtually all organs and tissues. The unexpected relationship between the antibacterial activity and the aggregation behavior in aqueous solution (i.e., lyotropic liquid-crystalline properties) was revealed through systematic studies on the antibacterial activity of the phosphonium salts as a novel class of cationic biocides.[1] Organophosphorus compounds are associated with antiviral,[2] anticancer,[3] antifungal,[4–7] and antibacterial[4–7] activities. These observations encouraged us to synthesize the above derivatives, as Schiff bases and thiazolidinone derivatives themselves have good antibacterial and antifungal activities.

RESULTS AND DISCUSSION

2-amino-10-oxo-5,10-dihydro-10λ^5-phenophosphazin-10-ol and substituted aromatic aldehydes were taken in 1:1 molar ratio in presence

Received 29 June 2007; accepted 30 July 2007.
Address correspondence to S. R. Lokhandwala, Department of Chemistry, Veer Narmad South Gujarat University, Surat 395 007, India. E-mail: snehal_sl@yahoo.co.in

of methanol as solvent to yield 2-[(substituted benzylidene)-amino]-10-oxo-5,10-dihydro-10-λ^5-phenophosphazin-10-ol which was subsequently reacted with Thyoglycollic acid in molar ration of 1:3 using DMF as solvent to give corresponding 3-(10-hydroxy-10-oxo-5,10-dihydro-10λ^5-phenophosphazin-2-yl)-2-(substituted phenyl)-thiazolidin-4-one (Scheme 1). Physical and analytical details of the compounds are given in Table I.



SCHEME 1

IR SPECTRA

The formation of Schiff base derivatives was identified by the disappearance of ν (N—H) absorption band at 1250–1340 cm^{-1} and thiazolidinone derivatives were identified by the disappearance of ν (C = N) stretching vibration at 1595–1610 cm^{-1} present in monoamino and Schiff base derivatives respectively. Moreover the ν (C = O) stretching vibration was observed at 1710–1750 cm^{-1}. The ν (C-S-C) stretching vibration and was observed at 700–750 cm^{-1}, which proves thiazolidinone nucleus. In phenophosphazine derivatives characteristic stretching vibration ν (P = O)[8] appeared at 1240–1250 $cm^{-1}$and ν (P—OH)[9] appeared at 910–1040 cm^{-1} (Table II).

NMR SPECTRA

^{1}H NMR spectra of 2-[(substituted benzylidene)-amino]-10-oxo-5,10-dihydro-10-λ^5-phenophosphazin-10-ol showed a benzylideneimine proton signal at δ 8.35 as singlet, which disappeared in thiazolidinone

TABLE I Analytical Data of 3-(10-Hydroxy-10-oxo-5,10-dihydro-10λ^5-phenophosphazin-2-yl)-2-(Substituted Phenyl)-Thiazolidin-4-One Compounds

Comp. no.	Molecular formula	Yield %	M.P. °C	Analysis % Found (Calc.)					Molecular weight
				C	H	N	S	P	
SN-01	$C_{22}H_{19}O_4N_2PS$	80.0	>300	60.28 (60.27)	4.39 (4.37)	6.40 (6.39)	7.31 (7.29)	7.06 (7.05)	438.437
SN-02	$C_{21}H_{16}O_3N_2PClS$	79.2	>300	56.96 (56.95)	3.66 (3.64)	6.32 (6.33)	7.24 (7.23)	6.99 (6.98)	442.856
SN-03	$C_{21}H_{16}O_3N_2PBrS$	76.4	>300	51.75 (51.76)	3.32 (3.31)	5.74 (5.75)	6.58 (6.56)	6.36 (6.34)	487.307
SN-04	$C_{23}H_{19}O_3N_2PS$	73.9	>300	63.60 (63.59)	4.42 (4.41)	6.46 (6.45)	7.38 (7.39)	7.13 (7.15)	434.448
SN-05	$C_{21}H_{16}O_5N_3PS$	75.2	>300	55.62 (55.63)	3.57 (3.56)	9.25 (9.27)	7.07 (7.05)	6.83 (6.82)	453.409
SN-06	$C_{27}H_{21}O_4N_2PS$	86.4	292	64.80 (64.79)	4.22 (4.23)	5.61 (5.60)	6.41 (6.40)	6.19 (6.18)	500.506
SN-07	$C_{23}H_{21}O_5N_2PS$	84.5	250	58.96 (58.97)	4.53 (4.52)	5.96 (5.98)	6.84 (6.83)	6.61 (6.59)	468.463
SN-08	$C_{22}H_{19}O_5N_2PS$	83.9	295	58.14 (58.15)	4.20 (4.21)	6.14 (6.16)	7.06 (7.05)	6.82 (6.81)	454.437
SN-09	$C_{21}H_{17}O_3N_2PS$	86.4	198	61.77 (61.76)	4.22 (4.20)	6.85 (6.86)	7.85 (7.87)	7.58 (7.56)	408.411
SN-10	$C_{23}H_{21}O_6N_2PS$	87.5	>300	57.04 (57.02)	4.35 (4.37)	5.79 (5.78)	6.62 (6.61)	6.39 (6.40)	484.462

TABLE II Assignment of Main IR Bands (cm^{-1}) of Thiazolidinone Derivatives of Phenophosphazine Compounds

Comp. no.	Molecular formula	R	(C═O) str.	(C—S—C) str.	(C—N) str.	(CH═CH) str.	(N—H) str.	(N—C—N) str.	(P═O) str.	(N═O) str.	(P—OH) str.	(C—Cl) str.	(C—Br) str.
SN-01	$C_{22}H_{19}O_4N_2PS$	4-OCH_3	1717	705	1015	1392	3225	1312	1245	—	911	—	—
SN-02	$C_{21}H_{16}O_3N_2PClS$	3-Cl	1742	716	1021	1412	3450	1320	1426	—	1040	752	—
SN-03	$C_{21}H_{16}O_3N_2PBrS$	3-Br	1751	753	1025	1410	3365	1315	1248	—	1035	—	596
SN-04	$C_{23}H_{19}O_3N_2PS$	CH=CH	1718	729	1014	1395	3325	1318	1246	—	926	—	—
SN-05	$C_{21}H_{16}O_5N_3PS$	2-NO_2	1723	744	1023	1401	3450	1320	1255	1530	990	—	—
SN-06	$C_{27}H_{21}O_4N_2PS$	3-OC_6H_5	1714	729	1028	1412	3500	1318	1254	—	1021	—	—
SN-07	$C_{23}H_{21}O_5N_2PS$	3-OC_2H_5 4-OH	1730	738	1027	1420	3221	1319	1249	—	1035	—	—
SN-08	$C_{22}H_{19}O_5N_2PS$	3-OCH_3 4-OH	1748	700	1024	1398	3265	1314	1249	—	976	—	—
SN-09	$C_{21}H_{17}O_3N_2PS$	H	1739.6	711.6	1028	1406	3295	1313	1254	—	922	—	–
SN-10	$C_{23}H_{21}O_6N_2PS$	3,5-OCH_3 4-OH	1715.2	745.6	1030	1412	3482	1312	1253	—	1011	—	—

TABLE III Antimicrobial Screening Data of Phenophosphazine Derivatives Containing Substituted Thiazolidinones

		Compound dose : 50 ppm					
		Zone of inhibition in mm					
Comp. no.	Molecular formula	S. Aureus	B. Subtilis	E. coli	S. typhi	C. Albicans	A. niger
SN-01	$C_{22}H_{19}O_4N_2PS$	6.0	14.5	5.5	12.0	9.5	5.0
SN-02	$C_{21}H_{16}O_3N_2PClS$	5.5	11.5	5.0	9.0	6.5	4.5
SN-03	$C_{21}H_{16}O_3N_2PBrS$	10.0	11.0	9.6	8.5	6.0	9.1
SN-04	$C_{23}H_{19}O_3N_2PS$	7.0	14.5	6.5	12.0	9.5	6.0
SN-05	$C_{21}H_{16}O_5N_3PS$	11.0	18.5	10.5	16.0	13.5	10.0
SN-06	$C_{27}H_{21}O_4N_2PS$	13.0	20.5	12.0	18.0	15.5	11.5
SN-07	$C_{23}H_{21}O_5N_2PS$	11.5	17.0	11.0	14.5	12.0	10.5
SN-08	$C_{22}H_{19}O_5N_2PS$	10.0	14.0	9.5	11.5	9.0	9.0
SN-09	$C_{21}H_{17}O_3N_2PS$	15.0	12.0	6.0	9.5	7.0	5.5
SN-10	$C_{23}H_{21}O_6N_2PS$	9.0	8.5	8.5	6.0	3.5	8.0
Streptomycin (Standard drug)	—	30	30	30	+30	—	—
Cotrimazole (Standard drug)	—	—	—	—	—	31	31

derivative. Instead of that, a characteristic proton signal at δ 5.90 appeared showing the presence of N—CH group. A proton signal at δ 2.0 was observed as singlet in each compound confirming the presence of P—OH. The other signals were observed in accordance with the substituent groups and confirming their presence which are summarized in Table IV.

TABLE IV Assignment of Main ^{1}H NMR Bands (δ) of Thiazolidinone Derivatives of Phenophosphazine Compounds

Comp. no.	Molecular formula	R	Assignments (δ)
SN-01	$C_{22}H_{19}O_4N_2PS$	4-OCH_3	3.8(s,1H,N-H);1.9(s,1H,P-OH); 5.90(s,1H,N-CH);3.37(d,2H,C-CH_2); 3.71(t,3H,C-OCH_3); 6.5–7.0(m,11H, Aromatic)
SN-02	$C_{21}H_{16}O_3N_2PClS$	3-Cl	3.6(s,1H,N-H);2.0(s,1H,P-OH); 5.91(s,1H,N-CH);3.36(d,2H,C-CH_2); 6.5–7.08(m,11H,Aromatic)
SN-03	$C_{21}H_{16}O_3N_2PBrS$	3-Br	3.7(s,1H,N-H);1.8(s,1H,P-OH); 5.88(s,1H,N-CH);3.40(d,2H,C-CH_2); 6.5–7.24(m,11H,Aromatic)
SN-04	$C_{23}H_{19}O_3N_2PS$	CH=CH	3.8(s,1H,N-H);1.8(s,1H,P-OH); 5.95(s,1H,N-CH);3.39(d,2H,C-CH_2); 7.59(s,1H,C-CH); 6.5–7.65(m,12H, Aromatic)
SN-05	$C_{21}H_{16}O_5N_3PS$	2-NO_2	3.65(s,1H,N-H);1.7(s,1H,P-OH); 5.92(s,1H,N-CH);3.36(d,2H,C-CH_2); 6.5–8.07(m,11H,Aromatic)
SN-06	$C_{27}H_{21}O_4N_2PS$	3-OC_6H_5	3.8(s,1H,N-H);1.9(s,1H,P-OH); 5.90(s,1H,N-CH);3.37(d,2H,C-CH_2); 6.5–7.21(m,16H,Aromatic)
SN-07	$C_{23}H_{21}O_5N_2PS$	3-OC_2H_5 4-OH	3.7(s,1H,N-H);2.0(s,1H,P-OH); 5.91(s,1H,N-CH);3.37(d,2H,C-CH_2); 3.96 (d,2H,C-CH_2); 4.9(s,1H,C-OH); 1.32(t,3H,C-CH_3);6.5–7.0(m,9H, Aromatic)
SN-08	$C_{22}H_{19}O_5N_2PS$	3-OCH_3 4-OH	3.6(s,1H,N-H);1.9(s,1H,P-OH); 5.90(s,1H,N-CH);3.37(d,2H,C-CH_2); 3.72(t,3H,C-OCH_3);5.1(s,1H,C-OH); 6.5–7.2(m,9H,Aromatic)
SN-09	$C_{21}H_{17}O_3N_2PS$	H	3.8(s,1H,N-H);1.7(s,1H,P-OH); 5.93(s,1H,N-CH);3.37(d,2H,C-CH_2); 6.5–7.14(m,12H,Aromatic)
SN-10	$C_{23}H_{21}O_6N_2PS$	3,5-OCH_3 4-OH	3.7(s,1H,N-H);1.9(s,1H,P-OH); 5.90(s,1H,N-CH);3.37 (d,2H,C-CH_2); 3.74(t,3H,C-OCH_3);4.7(s,1H,C-OH); 6.5–7.1(m,8H,Aromatic)

ANTIMICROBIAL ACTIVITY

Antimicrobial activity was carried out for the synthesized test compounds using Agar Cup method[10,11] which used Mueller-Hinton agar and Sabouraud Dextrose agar (pH-7.3 ± 0.2 at 25°C) for bacterial and fungal activity respectively and a dose of 50 ppm. Results of the antibacterial and antifungal activities measured as zone of inhibition (mm) for thiazolidinone derivatives of phenophosphazines against *S aureus* and *B Subtilis* (gram positive bacteria), *E coli* and *S Typhi* (gram negative bacteria), *Candida albicans* and *Aspergillus niger* (fungus) are summarized in Table III. The antimicrobial activities of these compounds were found to be exceeding than the corresponding Schiff base[12] derivatives of phenophosphazine. These compounds were compared to commercial antibacterial and antifungal drugs like Streptomycin and Cotrimazole. Among all the compounds, the antibacterial activity against *B Subtilis* was more prevalent. Compound SN-09 showed promising activity against *S Aureus* (50%) and Compound SN-06 showed promising activity against *B Subtilis* (68.3%), *E coli* (40%), *S Typhi* (60%), *C albicans* (50%) and *A niger* (37.1%) respectively as compared to the standard drugs.

EXPERIMENTAL

All commercial reagents and solvents were dried and distilled by common methods before use. Melting points were determined by capillary method and are uncorrected. The operations involving phosphorus compounds were carried out in dry equipment in nitrogen atmosphere. IR spectra were recorded on Perkin-Elmer 577 grating spectrometer in KBr discs in the region of 4000-200 cm^{-1}. NMR were recorded on JEOL FX-90Q spectrophotometer using $CDCl_3$ as solvent.

Synthesis of 3-(10-hydroxy-10-oxo-5,10-dihydro-10λ^5-phenophosphazin-2-yl)-2-(substituted phenyl)-thiazolidin-4-one

In a 250 ml round bottom flask, 2-[(4′-methoxy-benzylidene)-amino]-10-oxo-5,10-dihydro-10-λ^5-phenophosphazin-10-ol (3.6433 g, 10 mmol) and thioglycolic acid (2.76 g, 30 m mol) were dissolved in DMF (60 ml) as a solvent. The reaction mixture was refluxed for 10–12 h. Excess of solvent was then removed by distillation and cooled. The solid thus separated was filtered, washed, dried, and recrystallized with glacial acetic acid. The process was repeated using different substituted Schiff bases (10 mmol) to obtain different compounds.

CONCLUSION

It can be concluded from the above synthetic work that phosphorus if incorporated with the standard antimicrobial agents may enhance their activities. The results at primitive stage are satisfactory and it may be thought that phosphorus- containing antimicrobials may cover the broad spectrum in antimicrobial world.

REFERENCES

[1] A. Kanazawa and T. Ikeda, *Coordination Chem Reviews,* **198(1),** 117–131 (2000).
[2] S. S. Kadam, K. R. Mahadik, and K. G. Bothara, *Principles of Medicinal Chem*, **I,** 132 (2000).
[3] S. S. Kadam, K. R. Mahadik, and K. G. Bothara, *Principles of Medicinal Chem*, **I,** 154 (2000).
[4] A. Bijul Lakshman and R. L. Gupta, *Indian J of Chem*, **44B,** 152–157 (2005).
[5] P. Vasu Govardhana Reddy, C. Suresh Reddy, and M. Venugopal, *J. of Heteroatom Chem*, **14(6),** 509–512 (2003).
[6] K. Demarest, C. Shwender, and D. Wustrow, U.S. Patent, 5, 532, 226 (1996).
[7] M. F. Pharanath, S. Babu, U. Anasuyamma, C. Naga Raju, and C. Suresh Reddy, *J Heteroatom Chem*, **16(7),** 572–575 (2005).
[8] N. Kabra, V. Gupta, V. Kabra, S. Jain, and K. Bhatanagar, *Phosphorus, Sulfur and Silicon*, **178,** 851 (2003).
[9] B. Silverstein, G. Bassler, and T. Morril, *Spectrometric identification of organic compounds IV*, 176 (1963).
[10] S. C. Prescott and C. G. Dunn , *Industrial Microbiology*, 519 (1949).
[11] W. Burrow, *Textbook of Microbiology*, 8 (1954).
[12] A. K. Mittal and U. P. Singhal, *J Indian Chem Soc*, **LIX,** 373 (1982).