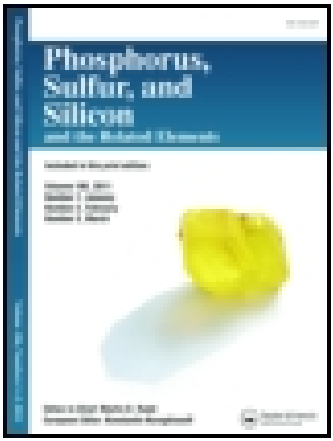

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

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Published online: 07 Oct 2008.

To cite this article: S. R. Lokhandwala & K. R. Desai (2008) Synthesis and Antimicrobial Activity of Substituted Phenophosphazines, Phosphorus, Sulfur, and Silicon and the Related Elements, 183:11, 2678-2684

To link to this article: http://dx.doi.org/10.1080/10426500801968144

Phosphorus, Sulfur, and Silicon, 183:2678–2684, 2008

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500801968144

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Synthesis and Antimicrobial Activity of Substituted Phenophosphazines

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Several Schiff base derivatives of phenophosphazines were synthesized by the reaction of amino phenophosphazines and aromatic aldehydes in equimolar ratio, using methanol as solvent. Possible structures have been proposed on the basis of elemental analysis, IR, and ^1H NMR spectral studies. The antibacterial and antifungal activities of the above mentioned Schiff base 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; Schiff base

INTRODUCTION

Enzymatically catalyzed phosphate-transfer reactions are numerous and vital in the metabolism of carbohydrate, lipid and protein, and a proper concentration of the anion is of primary importance in assuring an orderly biochemical sequence. Once phosphate gains access to the body fluids and tissues, it exerts little pharmacological effect. If the ion is introduced into the gastro-intestinal tract, the absorbed phosphate is rapidly excreted. If large amounts are given by this route much of it may escape absorption. This leads to cathartic action and therefore the phosphate salts are employed as mild laxatives.[1] Owing to the fungicidal,[2] antineoplastics,[3] antiviral,[4] antibacterial,[5] and antiarthritic[6] activity of phosphorus and its salts, above phenophosphazine derivatives were thought to be biologically active. Schiff bases also possess diversified biological activities like tuberculostatic, fungicidal[7] and bactericidal.[8] The biological activity of Schiff base derivatives has been attributed to azomethine linkage. A large number of Schiff bases are known to

Received 24 October 2007; accepted 31 January 2008.
The authors thank RSIC/CIL, Punjab University, Chandigarh for the spectral data and N. V. Patel College, Vallabh Vidyanagar, for antimicrobial studies.
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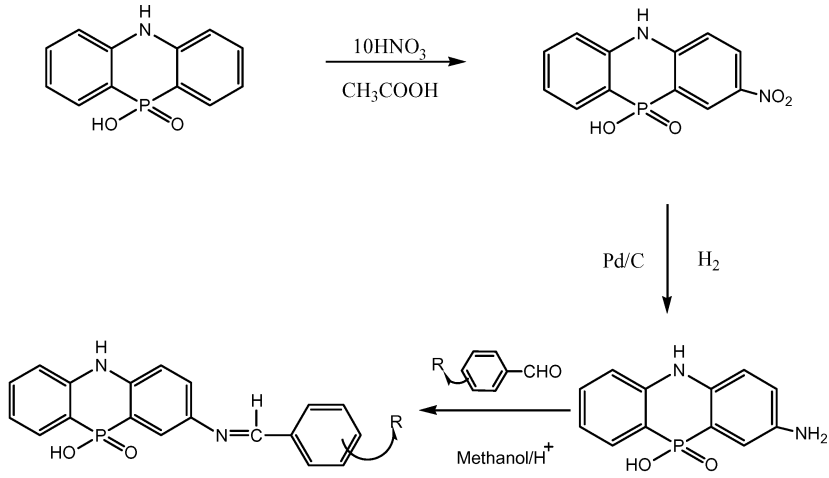
possess useful biological activities like antimicrobial,[9,10] fungicidal,[11] and bactericidal.[12,13]



SCHEME 1

RESULTS AND DISCUSSION

10-oxo-5,10-dihydro-10λ^5-phenophosphazine-10-ol[14] was nitrated utilizing nitric acid and acetic acid, which under pressure and in presence of Palladium-Carbon catalyst was reduced to 2-amino-10-oxo-5,10-dihydro-10λ^5-phenophosphazin-10-ol. The amino derivative and substituted aromatic aldehydes were dissolved in methanol in 1:1 molar ratio to yield 2-[(substitutedbenzylidene)-amino]-10-oxo-5,10-dihydro-10-λ^5-phenophosphazin-10-ol (Schiff base derivatives).The physical and analytical details of the compounds (01 to 10) are given in Table I.

IR Spectra

The formation of nitro derivative was identified by the appearance of ν (C—N) absorption band at 832–825 cm^{-1} which disappeared in amino compound with the appearance of ν (C—N) stretching vibration at 1345–1280 cm^{-1} present in monoamino derivative. The appearance of strong absorption band of ν (C=N) stretching vibration at 1710 cm^{-1} clearly indicated a Schiff base derivative. In phenophosphazine

TABLE I Analytical Data of 2-[(Substituted Benzylidene)-amino]-10-oxo-5,10-dihydro-10-λ^5-phenophosphazin-10-OL Compounds

Comp. no.	Molecular formula	Yield (%)	M.p. (°C)	Analysis % found (calcd.) C	H	N	O	P	Molecular Weight (gm)
01	$C_{20}H_{17}O_3N_2P$	78.2	>300	65.91 (65.93)	4.68 (4.70)	7.68 (7.69)	13.18 (13.17)	8.51 (8.50)	364.334
02	$C_{19}H_{14}O_2N_2PCl$	81.0	>300	61.92 (61.89)	3.85 (3.83)	7.62 (7.60)	8.70 (8.69)	8.38 (8.40)	368.753
03	$C_{19}H_{14}O_2N_2PBr$	75.1	298	55.22 (55.23)	3.41 (3.42)	6.77 (6.78)	7.73 (7.74)	7.51 (7.50)	413.200
04	$C_{21}H_{17}O_2N_2P$	83.0	280	70.20 (70.21)	4.78 (4.76)	7.79 (7.78)	8.86 (8.88)	8.62 (8.60)	360.346
05	$C_{19}H_{14}O_4N_3P$	63.5	>300	60.15 (60.16)	3.74 (3.72)	11.07 (11.08)	16.88 (16.87)	8.15 (8.17)	379.306
06	$C_{25}H_{19}O_3N_2P$	82.1	262	70.41 (70.42)	4.47 (4.49)	6.56 (6.57)	11.28 (11.26)	7.25 (7.26)	426.404
07	$C_{21}H_{19}O_4N_2P$	75.0	204	63.98 (63.96)	4.85 (4.86)	7.08 (7.10)	16.21 (16.23)	7.87 (7.85)	394.360
08	$C_{20}H_{17}O_4N_2P$	78.2	80	63.14 (63.16)	4.50 (4.51)	7.39 (7.37)	16.85 (16.83)	8.12 (8.14)	380.334
09	$C_{19}H_{15}O_2N_2P$	85.0	110	68.28 (68.26)	4.53 (4.52)	8.40 (8.38)	9.58 (9.57)	9.28 (9.27)	334.308
10	$C_{21}H_{19}O_5N_2P$	89.5	>300	61.48 (61.46)	4.68 (4.67)	6.85 (6.83)	19.48 (19.47)	7.56 (7.55)	410.360

derivatives characteristic stretching vibration ν (P═O)[15]appeared at 1240−1250 $cm^{-1}$and ν (P—OH)[16]appeared at 910−1040cm^{-1} (Table II).

NMR Spectra

^{1}H NMR spectra of 2-amino-10-oxo-5,10-dihydro-10λ^5-phenophosphazin-10-ol showed a proton signal at δ 4.0 as singlet which disappeared in Schiff base derivative. Instead, a characteristic benzylideneimine proton signal at δ 8.35 as singlet 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.

Antimicrobial Activity

The compounds were screened for their antibacterial and antifungal activities using dry diffusion technique and cup-borer[17,18] methods,

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

Comp. No.	(C═N) str.	(O—H) str.	(C—H) 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.
01	1712	3223	3018	1417	3342	1300	1238	—	912	—	—
02	1705	3330	3112	1400	3502	1320	1246	—	1045	761	—
03	1711	3212	2995	1425	3361	1315	1248	—	1035	—	589
04	1717	3321	3019	1418	3319	1318	1246	—	926	—	—
05	1713	3342	3002	1411	3482	1320	1255	1525	995	—	—
06	1711	3220	3010	1405	3460	1318	1254	—	1021	—	—
07	1720	3210	3039	1429	3221	1319	1249	—	1025	—	—
08	1705	3200	2990	1432	3268	1314	1249	—	976	—	—
09	1718	3224	3017	1417	3300	1313	1254	—	922	—	—
10	1678	3239	3042	1410	3450	1312	1253	—	1010	—	—

TABLE III Antimicrobial Screening Data of Imine Derivatives of Phenophosphazine Compounds

Comp. no.	Molecular formula	Compound dose : 50 ppm Zone of inhibition in mm					
		S Aureus	B Subtilis	E coli	S typhi	C Albicans	A niger
01	$C_{20}H_{17}O_3N_2P$	7	9.5	6.5	7	4.5	6
02	$C_{19}H_{14}O_2N_2PBr$	10	9	9.5	6.5	4	9
03	$C_{19}H_{14}O_2N_2PCl$	6.5	10	6	7.5	5	5.5
04	$C_{21}H_{17}O_2N_2P$	8	13.5	7.5	11	8.5	7
05	$C_{19}H_{14}O_4N_3P$	12	17.5	6	15	12.5	5.5
06	$C_{25}H_{19}O_3N_2P$	7	11	6.5	8.5	16	6
07	$C_{21}H_{19}O_4N_2P$	9.5	12	9	9.5	7	8.5
08	$C_{20}H_{17}O_4N_2P$	11.5	20.5	11	18	11	10.5
09	$C_{19}H_{15}O_2N_2P$	6	14.5	5.5	12	9.5	5
10	$C_{21}H_{19}O_5N_2P$	6.5	8	6	5.5	3	5.5
Streptomycin (Standard drug)		30	30	30	30	—	—
Streptomycin Standard drug)		—	—	—	—	31	31

respectively, at concentration 10 mg/mL. Mueller-Hinton Agar and Sabouraud Dextrose Agar were employed as culture media for these activities respectively using DMF as solvent. The title compounds were screened in vitro for their antibacterial activity against *S aureus* and *B Subtilis* (gram positive bacteria) and *E coli* and *S Typhi* (gram negative bacteria) and antifungal activity against *Candida albicans* and *Aspergillus niger* (fungus). The compounds showed potential antibacterial activity against *B Subtilis*. Compound SN-05 showed promising activity against *S Aureus* (40%) and Compound SN-08 showed promising activity against *B Subtilis* (68.33%) , *E coli* (36.67%), *S Typhi* (60%), *A niger* (35%), and compound SN-06 showed promising activity against *C albicans* (41.67%), respectively, as compared to the standard drugs (Table III).

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

TABLE IV ^{1}H NMR Data of Imine Derivatives of Phenophosphazine Compounds

Comp. no.	Assignments (δ)
01	1.8(s,1H,P—OH); 8.35(s,1H,N═CH);3.8(s,1H,N—H);3.72(t,3H,C—OCH_3);6.4–7.6 (m,11H,Aromatic)
02	2.1(s,1H,P—OH);8.36(s,1H,N═CH);3.7(s,1H,N—H);6.5–7.7(m,11H,Aromatic)
03	1.9(s,1H,P—OH);8.38(s,1H,N═CH);3.9(s,1H,N—H);6.4–7.7(m,11H,Aromatic)
04	2.0(s,1H,P—OH);7.52(s,1H,N═CH);4.1(s,1H,N—H); 5.5(s,1H,C—H); 6.7(s,1H,C—H); 6.5–7.3(m,12H,Aromatic)
05	1.7(s,1H,P—OH);8.38(s,1H,N═CH);4.0(s,1H,N—H);6.4–8.2(m,11H,Aromatic)
06	1.9(s,1H,P—OH);8.39(s,1H,N═CH);4.0(s,1H,N—H);6.4–7.3(m,16H,Aromatic)
07	1.9(s,1H,P—OH);8.38(s,1H,N═CH);3.9(s,1H,N—H); 1.33(t,3H,C—OCH_3);3.97(d,2H,C—CH_2); 4.9(s,1H,C-OH);6.4–7.0(m,10H,Aromatic)
08	2.0(s,1H,P—OH);8.34(s,1H,N═CH);3.92(s,1H,N—H); 3.74(t,3H,C—OCH_3);5.1(s,1H,C—OH); 6.5–7.1(m,10H,Aromatic)
09	1.8(s,1H,P—OH);8.36(s,1H,N═CH);4.0(s,1H,N—H);6.4–7.6(m,12H,Aromatic)
10	1.9(s,1H,P—OH);8.40(s,1H,N═CH);3.93(s,1H,N—H); 3.72(t,3H,C—OCH_3);5.0(s,1H,C—OH); 6.5–7.0(m,9H,Aromatic)

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 2-Nitro-10-oxo-5,10-dihydro-10λ^5-phenophosphazin-10-ol

10-oxo-5,10-dihydro-10λ^5-phenophosphazine-10-ol (4.92 g, 20 mmol) was dissolved in acetic acid (127 mL, 2000 mmol) at 100°C. The solution was cooled to room temperature and a mixture of nitric acid (50 mL, 600 mmol) and acetic acid (12.3 mL, 2000 mmol) were added at such a rate that the temperature of the reaction mixture did not rise above 20°C. The reaction mixture was stirred overnight at 15–20°C, and the mixture was poured in 1 liter of ice cold water. The reaction mixture was filtered out and recrystallized from acetic acid (50 mL).

Synthesis of 2-Amino-10-oxo-5,10-dihydro-10λ^5-phenophosphazin-10-ol

2-nitro-10-oxo-5,10-dihydro-10λ^5-phenophosphazin-10-ol (5.52 g, 20 mmol) was suspended in methanol and the pH was adjusted to 7.2 using methanolic KOH (10%). The reaction mixture was refluxed for 6 h at room temperature under pressure in presence of 5% Pd/C

(748 mg). The catalyst and the solvent were removed to give solid which was dissolved in 150 mL of water. The solution was stirred with charcoal at 60°C for 45 min and filtered to remove charcoal. The filtrate was then acidified to pH = 6 using 2N HCl, and the precipitates were collected over water.

Synthesis of 2-[(4′-Methoxy-benzylidene)-amino]-10-oxo-5,10-dihydro-10-λ^5-phenophosphazin-10-ol

2-amino-10-oxo-5,10-dihydro-10λ^5-phenophosphazin-10-ol (4.92 g, 20 mmol) and p-methoxy benzaldehyde (2.4 mL, 20 mmol) were dissolved in methanol. The reaction was refluxed for 6−8 h in presence of acid catalyst. The reaction mixture was then filtered, washed, dried, and recrystallized from hot methanol (35 mL). The process was repeated using different substituted aldehydes (20 mmol) to obtain different compounds.

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