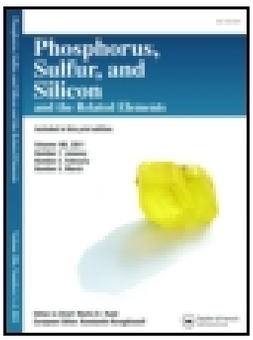

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Synthesis and Structure of Novel Phosphorylated Azomethines

Irina V. Galkina,[1] Elmira R. Kiyamova[1], Aynaz Z. Gaynullin,[1] Dmitriy I. Bakhtiyarov,[1] Marina P. Shulaeva,[2] Oskar K. Pozdeev,[2] Svetlana N. Egorova[2], Kamil A. Ivshin[1], Olga N. Kataeva[1], Yuliya V. Bakhtiyarova[1], Ayrat R. Garifzanov,[1] Vladimir I. Galkin[1]

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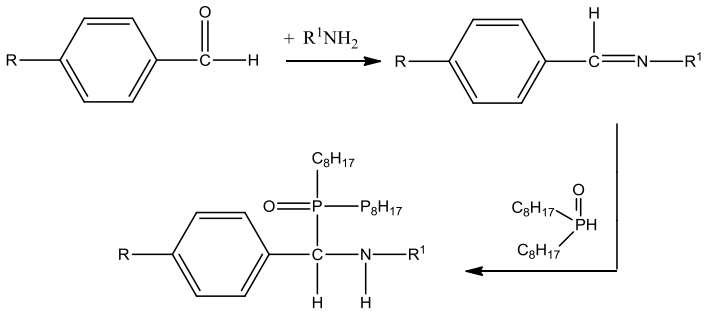
GRAPHICAL ABSTRACT



R = Br, NO_2
$R^1 = C_{16}H_{33}, C_{18}H_{37}$

Abstract *The condensation of do-, hexa-, octadecan-1-amines with bromo- and nitrobenzaldehydes yielded a series of Schiff bases in good yields. Subsequent reaction of these compounds with dioctylphosphine oxide yielded phosphorylated azomethines and some were characterized using X-ray crystallography. The structure of the isolated compounds was determined by IR and NMR spectroscopy, elemental analysis, and their thermal stability was studied by simultaneous thermogravimetry and differential scanning calorimetry. All of the*

synthesized compounds were tested for their antibacterial and anti-Candida activity. A number of the compounds exhibited antimicrobial activity comparable to that of the commercially available drugs, ciprofloxacin and clotrimazole.

Keywords Phosphorylated Schiff bases; organophosphorus compounds; antimicrobial activity

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ACCEPTED MANUSCRIPT

INTRODUCTION

Azomethines and their phosphorylated products with aliphatic long-chain, due to their unique reactivity, are important in the construction of various multifunctional compounds with a broad spectrum of biological activity[1-6]. However, literature survey has indicated that all obtained by us phosphorylated Schiff bases have not been synthesized and their biological activities have not been tested.

RESULTS AND DISCUSSION

Phosphorylated Schiff bases 5-8 of saturated benzaldehydes were synthesized by the reaction of dioctylphosphine oxide with Schiff bases 1-4 derived by the condensation of hexa-, octadecan-1-amines with bromo- and nitrobenzaldehydes as shown in scheme 1 respectively.

We have found that the amination of 4-bromo- and 4-nitrobenzaldehydes with long-chain aliphatic amines ie hexa- and octadecan-1-amines in ratios in ethanol–diethyl ether (1:3) at room temperature under vigorous stirring gave products of condensation – azomethines 1-4. Heating in ethanol these compounds leads to the formation of products 5-8. The structure of the isolated compounds was determined by IR and NMR spectroscopy, elemental and X-ray analysis; their thermal stability was studied by simultaneous thermogravimetry and differential scanning calorimetry. All of the synthesized compounds were fully characterized by physical data in Table 1.

The structure of compound 3 was confirmed by X-ray analysis (Fig. 1.).

The antibacterial and antifungal activity of a series of azomethines (1-4) and their phosphorylated products (5-8) were investigated *in vitro* against several pathogenic

representative Gram-negative bacteria (*Pseudomonas aeruginoza* ATCC 27853 and *Escherichia coli* ATCC 25922), Gram-positive bacteria (*Staphylococcus aureus* ATCC 29213 and *Bacillus cereus* ATCC 11778), and pathogenic fungi *Candida albicans* ATCC 885-653. The results were summarized in Table 2.

Cup-plate Agar method was used for evaluation of antibacterial activity. The nutrient agar medium is used. The medium with bacteria was poured into sterilized Petri dishes under aseptic conditions. Standard drugs were Chlorhexidine (50 µg/0.1 mL) and test compounds at concentration of 50 µg/0.1 mL. Solvent used was mixture of water and isopropanol at different ratios (1:10). Plates were incubated at 37^{o}C for 24 hours. The antifungal activity was carried out by using cup-plate method using Sabouraud's agar medium. The standard drug used was Griseofulvin (50 µg/0.1 mL) and the test compounds at concentration of 50 µg/0.1 mL by using of the mixture of solvents–ethanol – water at different ratios (1:10). After incubation the average of inhibition was recorded in mm.

The synthesized compounds exhibited moderate antimicrobial activities *in vitro*. Especially, compounds 1 and 3 with hexadecylalkyl chain showed the most potent antibacterial and antifungal activities as compared to Chlorhexidine and Griseofulvin as reference drugs, against *Staphylococcus aureus, Escherichia coli, Bacillus cereus, Pseudomonas aeruginoza* and *Candida albicans.*

CONCLUSIONS

In conclusion, new Schiff bases and their phosphorylated compounds were synthesized and their structures were determined by IR, NMR, TG-DSC and X-ray analyses. The

antimicrobial activity was measured. We have also reported the first crystal structures of these compounds.

EXPERIMENTAL

All chemicals purchased from Sigma-Aldrich were reagent grade and used without purification. IR spectra were taken on a spectrophotometer Specord 251R in the range 400-3700 cm^{-1} from mulls in mineral oil between KBr plates. ^{31}P NMR spectra were registered on a spectrometer Bruker Avance-400. Chemical shifts were determined with respect to external reference, 85% H_3PO_4. The purity and thermal stability of crystal compounds were determined by simultaneous TG/DSC analysis on a NETZSCH STA 449C instrument (temperature range 20-400^oC, heating rate 10 deg/min, argon atmosphere).

General procedure for the synthesis of phosphorylated azomethines - N-(4-bromo- or nitrobenzylidene)alkyl-1-amines 1-4.

A series of Schiff bases (1-4) were synthesized by the condensation of do-, hexa-, octadecan-1-amines with bromo- and nitrobenzaldehydes in good yields in ethanol. The reaction mixture was left overnight at room temperature, wherein the crystals of the product were precipitated out. The crystals were collected by suction filtration, washed with EtOH and dried.

General procedure for the synthesis of phosphorylated azomethines - (R)-((4-bromo- or nitrophenyl)(alkylamino)methyl)dioctylphosphine oxides 5-8.

Phosphorylated Schiff bases (5-8) were synthesized by the reaction of dioctylphosphine with Schiff bases (1-4) in ethanol. A suspension was refluxed for 16 h. The reaction mixture was left overnight at room temperature, wherein the crystals of the product were precipitated out. The crystals were collected by suction filtration, washed with EtOH and dried.

Supplementary Materials

X-ray Structure Determination (XRD)

A data set for single crystal of $C_{25}H_{42}N_2O_2$ 4 was collected on a Bruker AXS Kappa APEX Duo diffractometer with graphite-monochromated Cu Kα radiation (λ= 1.54178 Å) at T = 198(2) K. Crystal size 0.054 mm x 0.149 mm x 0.494 mm. Programs used: data collection APEX2[7], data reduction SAINT[8], structure solution SHELXS97[9], structure refinement by full-matrix least-squares against F^2 using SHELXL-97[9].

Crystal data for $C_{25}H_{42}N_2O_2$, M = 402.6 g/mol, monoclinic, space group *P2(1)* (No. 4), Z = 4, a = 4.6112(6) b = 80.735(11)c = 6.5786(8) Å, V = 2377.2(5) $Å^3$, ρ_{calc} = 1.125 $g \cdot cm^{-3}$, μ=0.543 mm^{-1}, multi-scan absorption correction was applied using SADABS[10], 33313 reflections collected ($\pm h$, $\pm k$, $\pm l$), θ range = 1.09^0 to 52.67^0, 4949 independent (R_{int} = 0.0402) and 4690 observed reflections [$I \geq 2\ \sigma(I)$], 523 refined parameters, R = 0.0693, wR^2 = 0.2365, max. residual electron density 0.269 (-0.312) e $Å^{-3}$. Completeness is low because of the weakly diffracting thin plate under Cu-radiation.

Crystallographic data for the structural analysis of compound 4 has been deposited at the Cambridge Crystallographic Data Center (CCDC number 1486043). Copies of the information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1 EZ, UK (Fax: + 44-1223-336033; email: deposit@ccdc.cam.ac.uk or www.ccdc.can.ac.uk).

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Table 1. Physical data for the Schiff bases 1-4 and their corresponding phosphorylated compounds 5-8

Compound	Mw (g/mol)	Yield (%)	Empirical formula	Found (calc) (%)				m.p. (^{o}C)
				C	H	N	P	
1	407.9	82	$C_{23}H_{38}BrN$	67.53 (67.66)	9.41 (9.32)	3.57 (3.43)	-	44.1
2	435.9	79	$C_{25}H_{42}BrN$	69.11 (68.82)	9.87 (9.64)	3.03 (3.21)	-	57.2
3	374	71	$C_{23}H_{38}N_2O_2$	74.07 (73.80)	9.87 (10.16)	7.77 (7.49)	-	69.9
4	402	78	$C_{25}H_{42}N_2O_2$	74.58 (74.63)	9.99 (10.45)	7.09 (6.97)	-	60.8
5	681.9	77	$C_{39}H_{73}BrNOP$	69.03 (68.63)	11.03 (10.71)	2.33 (2.53)	4.27 (4.55)	oil
6	709.9	81	$C_{41}H_{77}BrNOP$	69.76 (69.31)	10.97 (10.85)	2.03 (1.97)	4.03 (4.37)	oil
7	648	76	$C_{39}H_{73}N_2O_3P$	72.01 (72.22)	11.43 (11.27)	4.67 (4.32)	4.87 (4.78)	oil
8	676	82	$C_{41}H_{77}N_2O_3P$	73.13 (72.78)	11.57 (11.39)	4.03 (4.14)	4.63 (4.59)	oil

Table 2. Antimicrobial activity (growth inhibition zone, mm) of compounds (c = 50 µg/0.1 mL)

Compound	*Staphylococcus aureus*	*Escherichia coli*	*Bacillus cereus*	*Pseudomonas aeruginosa*	*Candida albicans*
1	28	25	45	30	32
2	26	21	33	19	30
3	60	31	48	27	29
4	28	19	31	17	27
5	25	17	13	15	29
6	21	25	13	21	26
7	23	18	15	13	22
8	19	17	11	16	24
Chlorhexidine	16±0.5	15±0.2	10±0.3	8±0.1	19-
Griseofulvin	0	0	0	0	19±02

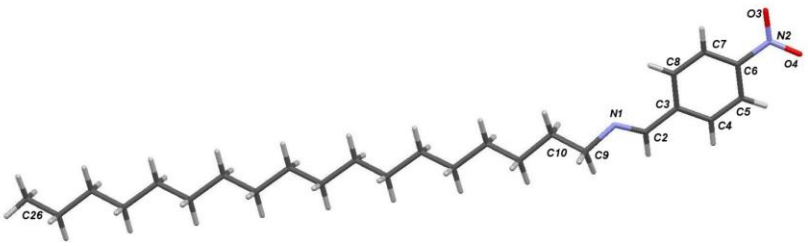
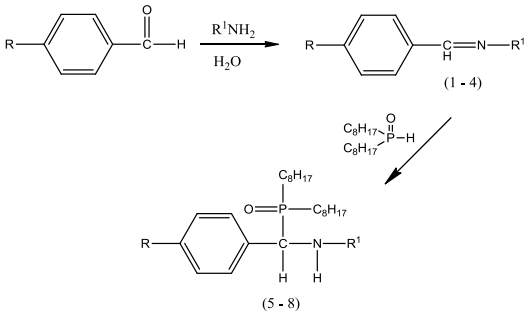


Figure 1. Geometry of the molecule of crystal 4 - N-(4-nitrobenzylidene)octadecan-1-amine



(1, 5) R = Br, $R^1 = C_{16}H_{33}$
(2, 6) R = Br, $R^1 = C_{18}H_{37}$

(3, 7) R = NO_2, $R_1 = C_{16}H_{33}$
(4, 8) R = NO_2, R_1 - $C_{18}H_{37}$

Scheme 1