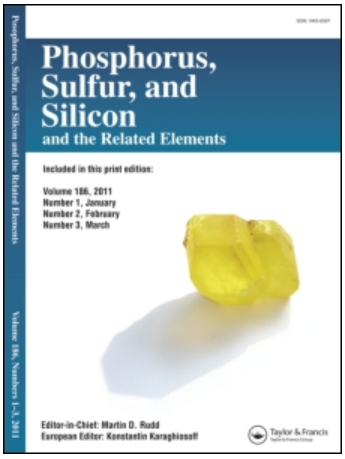

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SYNTHESIS AND BIOLOGICAL STUDIES OF SOME NOVEL CYCLODIPHOSPHAZANES

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SYNTHESIS AND BIOLOGICAL STUDIES OF SOME NOVEL CYCLODIPHOSPHAZANES

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Interaction of hexachlorocyclodiphosphazanes (Ia-f) and 2,4-dithio-2,4-dichlorocyclodiphosphazane derivatives (IIa–f) with diphenyl-(4-dimethyl amino phenyl) methanol (III) and 2,3-dihydroxy naphthalene (IV) has been described. The structures of the cyclodiphosphazane derivatives (Va-l) and (VIa-l) were proposed on the basis of microanalytical data, IR, Mass spectra, ^{1}HNMR and ^{31}P NMR spectra. The biological activity of these compounds was studied on different microorganisms.

INTRODUCTION

The reaction of hexachlorocyclodiphosphazanes (I) with amino compounds has been investigated in great detail. [1-8] It was reported also that the reaction of hexachlorocyclodiphosphazanes with bifunctional reagents (such as urea, thiourea and amino acids) furnished geminal and non-geminal amino cyclodiphosphazanes. [9-11] Analogous reactions with compounds containing the hydroxyl group have received less attention.

The aim of the present work is to extend the scope of the reaction of the prepared cyclodiphosphazanes to cover reactions with mono- and bifunctional reagents such as diphenyl- (4-dimethylamino phenyl) methanol and 2,3-dihdroxy naphthalene as compounds containing the hydroxyl group.

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EXPERIMENTAL

Microanalytical determinations were carried out by the Microanalytical Laboratory, Cairo University. Phosphorus was determined gravimetrically as phosphoammonium molybdate using R.Voy method. [12] The mid-infrared and the Ultraviolet measurements have been carried out at the Chemistry Department, Faculty of Science, Al-Azhar University. The mid-infrared spectra were recorded on a Shimadzu-440 Infrared Spectrophotometer using the KBr technique. Ultraviolet spectra were recorded on a Perkin Elmer Lambda-3B UV-VIS. spectrophotometer using dimethyl sulfoxide as the solvent. ^{1}H NMR spectra were measured on a Varian EM-360-90 MHz spectrophotometer using TMS as an internal standard. Chemical shifts (δ) are in ppm. ^{31}P NMR spectra were obtained on a JEOL JNM-Ex270 spectrometer. The mass spectra were performed by Shimazu-Ge-Ms-Qp 100 EX using the direct inlet system, Cairo University. The reported uncorrected melting points were measured using a Griffen melting point apparatus, England.

Synthesis of Hexachlorocyclodiphosph(v)azane Derivatives (Ia-f)

Hexachlorocyclodiphosph(v)azane derivatives (Ia-f) have been prepared and purified using the method described previously. [13-15]

Synthesis of Cyclodiphosph(v)azane Derivatives (Va-f) and (VIa-f)

Diphenyl-(4-dimethyl amino phenyl) methanol (III) or 2,3-dihydroxy naphthalene (IV), (0.2mol) was added in small portions to well-stirred cold solutions of hexachlorocyclodiphosph(v)azanes (Ia-f, 0.1mol) in 50 ml benzene during a half hour period under a nitrogen atmosphere. After the addition was completed, the reaction mixture was refluxed for two hours with continuous stirring. After complete evoluation of HCl gas, the reaction mixture was filtered hot. The solid obtained after cooling was filtered, washed several times with benzene and diethylether and dried in vacuo to give the corresponding cyclodiphosph(v)azane derivatives (Va-f) and (VIa-f). The yield of the products, melting points, and analytical data are listed in Table (I).

Synthesis of Dithio Cyclodiphosph(v)azane Derivatives(IIa-f)

2,4-Dithio-2,4-dichlorocyclodiphosphazane derivatives (IIa-f) have been prepared and purified using the method described previously. [16]

TABLE I Analytical Data of Prepared Cyclodiphosph(V)azane derivatives (Va-l) and (VIa-l).

Cpd. No Molecular Formula	Yield %	m.p. Ĉ	Elemental Analyses, Calculated/Found C%	H%	N%	P%	δ max.
Va	$C_{54}H_{50}Cl_4N_4O_2P_2$	65 142	65.4/65.1	5/4.5	5.6/5.9	6.2/5.8	265
Vb	$C_{56}H_{54}Cl_4N_4O_2P_2$	67 110	66.0/65.9	5.3/5.2	5.5/5.8	6.0/6.5	275
Vc	$C_{54}H_{48}Cl_6N_4O_2P_2$	70 123	61.1/61.5	4.5/4.1	5.2/4.8	5.8/6.3	265
Vd	$C_{54}H_{48}Cl_6N_4O_2P_2$	77 90	61.1/61.3	4.5/4.8	5.2/5.6	5.8/5.7	280
Ve	$C_{54}H_{48}Cl_4N_6O_2P_2$	76 153	63.7/62.8	7.7/7.2	8.2/7.9	6.0/6.5	269
Vf	$C_{54}H_{44}Br_2Cl_4N_8O_{10}P_2$	60 119	48.8/48.6	3.3/3.5	8.4/8.9	4.6/5.0	287
Vg	$C_{54}H_{50}N_4O_2P_2S_2$	56 118	71.0/70.6	5.4/5.6	6.1/6.5	6.7/7.1	290
Vh	$C_{56}H_{54}N_4O_2P_2S_2$	60 172	71.4/71.1	5.7/5.9	5.9/6.3	6.5/6.1	271
Vi	$C_{54}H_{48}Cl_2N_4O_2P_2S_2$	56 133	66.0/66.3	4.8/4.3	5.7/5.9	6.3/6.8	271
Vj	$C_{54}H_{48}Cl_2N_4O_2P_2S_2$	72 126	66.0/66.5	4.8/5.1	5.7./6.2	6.3/6.7	280
Vk	$C_{54}H_{48}N_6O_6P_2S_2$	66 196	64.6/64.1	4.7/4.2	8.3/8.5	6.1/5.8	285
Vl	$C_{54}H_{44}Br_2N_8O_{10}P_2S_2$	58 107	51.8/51.5	3.5/3.9	8.9/9.3	4.9/5.1	285
VIa	$C_{32}H_{22}Cl_2N_2O_4P_2$	68 165	60.8/60.2	3.4/3.7	4.4/3.9	9.7/10.2	275
VIb	$C_{34}H_{26}Cl_2N_2O_4P_2$	77 290	61.9/61.7	3.9/3.4	4.2/3.8	9.3/9.6	275
VIc	$C_{32}H_{20}Cl_4N_2O_4P_2$	67 150	54.8/54.6	2.8/3.1	4.0/3.8	8.8/9.2	265
VId	$C_{32}H_{20}Cl_4N_2O_4P_2$	78 180	54.8/54.3	2.8/2.5	4.0/4.5	8.8/8.9	270
VIe	$C_{32}H_{20}Cl_2N_4O_8P_2$	66 120	44.3/44.1	2.7/3.2	7.7/8.1	8.5/8.1	270
VIf	$C_{32}H_{16}Br_2Cl_2N_6O_{12}P_2$	69 160	39.6/39.2	1.6/1.5	8.6/9.1	6.3/5.8	278
VIg	$C_{32}H_{24}N_2O_4P_2S_2$	56 185	61.3/61.2	3.8/3.4	4.4/3.9	9.8/10.3	270
VIh	$C_{34}H_{28}N_2O_4P_2S_2$	58 265	62.3/61.8	4.2/4.7	4.2/4.6	9.4/8.9	280
VIi	$C_{32}H_{22}Cl_2N_2O_4P_2S_2$	67 170	55.2/54.9	3.1/3.5	4.0/3.8	8.8/8.5	285
VIj	$C_{32}H_{22}Cl_2N_2O_4P_2S_2$	59 230	55.2/54.9	3.1/2.8	4.0/3.7	8.8/9.2	290
VIk	$C_{32}H_{22}N_4O_8P_2S_2$	58 245	53.6/53.1	3.0/2.7	7.8/8.1	8.6/8.5	285
VIl	$C_{32}H_{18}Br_2N_6O_{12}P_2S_2$	57 270	39.8/39.6	1.8/1.6	8.7/9.2	6.4/6.9	288

Synthesis of Cyclodiphosph(v)azane Derivatives (Vg-l) and (VIg-l)

Diphenyl-(4-dimethyl amino phenyl) methanol (III) or 2,3-dihydroxy naphthalene (IV), (0.2mol) was added in small portions to well-stirred cold solutions of dithio cyclodiphosph(v)azane derivatives (IIa-f), 0.1 mol, in 50 ml acetonitrile using the same procedure as that mentioned for the preparation of cyclodiphosph(v)azane derivatives (Va-f) and (VIa-f). The analytical data are listed in Table (I).

Biological Screening of the Prepared Compounds

The minimum inhibitory concentration (MIC) was determined for each test Organism used individually.

Bacteria and Fungi

Bacteria employed were bacillus subtilis NCTC 8236, bacillus punillus NCTC 8241 micrococcus luteus ATCC 9341, staphylococcus aureus NCTC 7447, e. coli BPP01, pseudomonas aeruginosa ATCC 10145 and klebsiella pneumonia NC1B 9111, while fungi were candida albicans IMRU 3669, saccharomyces cerevesiae, aspergillus fumigatus, a.niger, a.terrcus f., penicillium citricus and p. citricus f. (fungal isolates were provided by the Mycology Lab., Faculty of Science, Al-Azhar University).

RESULTS AND DISCUSSION

The interaction of phosphorus pentachloride with aniline, p-toluidine, o and p-chloroaniline, o-nitroaniline and 2,4-dinitro-6-bromoaniline in dry benzene as a solvent produced hexachlorocyclophosph(v)azanes of type (Ia-f). [13-15] Structural elucidation of the prepared compounds (Va-l) and (VIa-l) was accomplished on the basis of elemental analysis (Table I), IR, UV-VIS. spectra, ^{1}H NMR and ^{31}P NMR spectroscopic data, and mass spectra.

Infrared spectra of these compounds showed characteristic νP-N, νP-Cl, νP-O-C (phenyl) and νP=S absorption bands, which are summarized in Table (II). A very strong absorption band observed in the 540-480 cm^{-1} region which is assigned to the P-Cl_2 antisymmetric stretch. [17-19] The absorption band in the 1020-1170 cm^{-1} region is attributed to the P-N stretch, [20] while the P-O-phenyl linkage gives rise to two absorption bands. A strong absorption band at 1260-1160 cm^{-1} is mainly due to the stretching of the C-O of the phenoxy group, and a strong absorption band at 994-914 cm^{-1} is assigned to stretching of the P-O bond in pentavalent phosphorus compounds. [17-18] The P=S band varies in intensity making its identification difficult in the infrared spectra. The P=S stretching vibration is expected to interact mechanically with attached P-O and P-C stretching vibrations at 850-650 cm^{-1}. The stretching frequency corresponding to a free OH was not observed for the prepared compounds (Va-f) and (VIa-f) thus indicate the proposed structure of the prepared compounds.

The mass spectra of the investigated compounds showed fragmentation patterns which were consistent with the proposed structures. The mass spectra of (Vd) showed m/e 455 (M^+,$C_{12}H_8N_2P_2Cl_6$), 302 (M^+,$C_{21}H_{20}NO$), 227 (M^+, $C_6H_4NPCl_3$), 111(M^+,C_6H_4Cl), and m/e 120 (M^+,$C_8H_{10}N$). The mass spectra of (VIa) showed m/e 347 (M^+,$C_{12}H_{10}N_2P_2Cl_2$), 142 (M^+,$C_{10}H_6O$), 122 (M^+,C_6H_5NP), 91 (M^+,C_6H_5N), while the mass spectra of (VIb) showed m/e 224 (M^+,$C_{10}H_6O_2PCL$), 171(M^+,C_7H_7NPCl), 142 (M^+,$C_{10}H_6O$), and 105 (M^+,C_7H_7N). It should be noted that the parent peak of all these compounds does

TABLE II Characteristic Infrared Stretching Vibrations of Cyclodiphosph(v)azane derivatives (Va-l) and (VIa-l).

Cpd. No.	Stretching Frequency cm^{-1}					
	ν P-N	ν P-Cl	ν P-O	ν C-Ophenoxy	ν P=S	ν OH
Va	1080	500	940	1160	—	—
Vb	1090	480	950	1164	—	—
Vc	1090	490	965	1161	—	—
Vd	1061	498	969	1162	—	—
Ve	1130	498	950	1170	—	—
Vf	1110	490	935	1195	—	—
Vg	1078	485	992	1179	700	—
Vh	1092	—	990	1200	710	—
Vi	1090	—	920	1220	705	—
Vj	1092	—	917	1231	702	—
Vk	1120	—	916	1225	720	—
Vl	1110	—	920	1232	650	—
VIa	1020	497	990	1167	—	—
VIb	1032	506	994	1160	—	—
VIc	1108	489	991	1162	—	—
VId	1103	528	925	1196	—	—
VIe	1125	525	950	1220	—	—
VIf	1110	498	965	1230	—	—
VIg	1025	—	990	1180	710	3450
VIh	1030	—	960	1210	705	3500
VIi	1110	—	950	1235	700	3450
VIj	1115	—	940	1219	690	3550
VIk	1130	—	945	1240	665	3460
VIl	1120	—	956	1225	695	3465

not appear in the spectra, presumably owing to the fact that these ions are meta stable and hence do not appear.

The UV spectra of the prepared compounds show a characteristic band at 270-290 nm corresponding to n-π^* transition within the phosphazane four-membered ring [21] of the dimeric structure, as shown in Table (I).

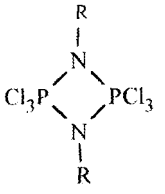
Further insight concerning the structure of these products was gleaned from a consideration of their ^1H NMR and ^{31}P NMR spectra. The ^1H NMR spectra of the cyclodiphosphazane derivatives (Va-l) and (VIa-l) showed the characteristic aromatic protons signals ranges at δ 6.25-8.12, the singlet at δ 2.85-2.9 is due to the proton of $N(CH_3)_2$ in addition to the signal at δ 2.25-2.44 characteristic of the proton of the methyl group for compounds (Vb), (Vh), (VIb) and (VIh). The ^1H NMR spectra of the compound (Va) dissolved in (DMSO-d_6) showed δ 7.6 (S, 10H, aromatic C-H), δ 6.26, 5.9 (d, 2H, dimethyl amino phenyl-H), δ 2.9 [S, 6H, $N(CH_3)_2$] with the absence of a peak at δ 4.13 due to free (OH) group of the hydroxy compound (III). This assignment is confirmed by the disappearance of

TABLE III MIC (Mg/ml) of some of the prepared Cyclodiphosphazane derivatives (Va-l) and (VIa-l).

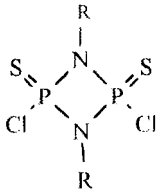
Organism	Va	Vd	Vg	Vj	VIa	VIb	VIc	VId
Bacillus subtilis NCTC 8236	3	-ve	8	-ve	5	15	3	10
Bacillus Pumillus NCTC 8241	3	-ve	8	-ve	5	15	3	10
Micrococcus luteus ATCC 9341	3	-ve	8	-ve	5	15	3	10
Staphylococcus aureus NCTC 7447	4	-ve	8	-ve	10	15	5	12
Escherichia coli BPPOI	8	-ve	-ve	-ve	10	13	5	8
Pseudomonas aeruginosa ATCC 10145	-ve	-ve	-ve	-ve	-ve	-ve	5	8
Klebsiella pneumonia NCIB 9111	8	-ve	-ve	-ve	10	15	5	8
Candida albicans IMRU 3669	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve
Saccharomyces Cerevisiae	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve
Aspergillus fumigatus	-ve	-ve	-ve	-ve	35	35	25	45
Aspergillus niger	-ve	-ve	-ve	-ve	40	40	25	50
Aspergillus terreus F	25	-ve	-ve	-ve	35	35	25	20
Penicillium citricus	30	-ve	50	35	35	-ve	20	25
Penicillium citricus F	30	-ve	50	35	35	-ve	20	25

the same peak after using D_2O. While the ^1H NMR spectra of the compound (VIa) dissolved in (DMSO-d_6) showed δ 8.24 (d, 2H, diphenoxy phenyl-H) δ 7.24, 7.32 (m, 10, aromatic-H), δ 7.2-7.6 (d,4H, Naphthalene-H), and the disappearance of a peak due to the OH group at δ 10.08 of the parent compound (IV). The ^{31}PNMR spectra of compound (VIg) showed a strong band at $\delta = -2.05$ indicating that the group (C_6H_5N-) coupled with the equivalent ^{31}P nuclei, thus demonstrating the presence of the arrangement N.P.N.P.

The compounds under investigation (Va-l) and (VIa-l) showed outstanding biological activity, Table (III), against different microorganisms. In chemical structure point of view of the prepared compounds with their effects on microbial tested, there is no obvious reason on what and which the sulfur element can affect the microbial growth or even the mechanism of these action. The similarities of compounds or analogues of each pair make it a suitable criteria for the results given in Table (III). Compound No.Vd is similar to Vj except the substitution of two chlorine atoms by sulfur, but their activities on microorganisms were the same (irrespective of compound Vd on penicillium citricus and p.citricum F). Analogues Vg and Va are like the former pair, but the activities on microorganisms were greatly different. The compound Va was anti-gram positive and gram negative bacteria compared with compound Vg (irrespective of pseudomunas aeruginosa ATCC 1014 S), the potency of activity may be compared to Cl^{-1} instead of S^{-2} in compound Vg. All the other compounds which have the same criteria showed the same effect on growth of micro-organism such as compounds Vg and Va. It is clear from the calculation of MIC

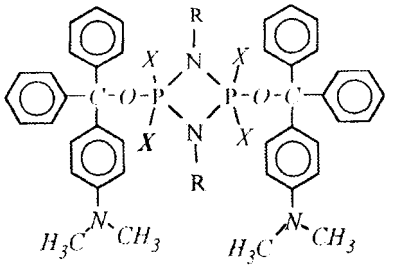


(Ia-f)

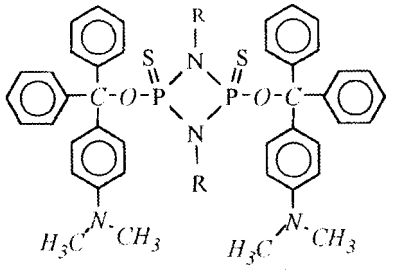


(IIa-f)

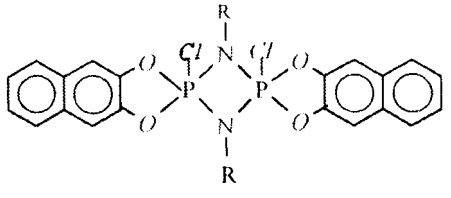
a, R= C_6H_5-
b, R= 4-$CH_3C_6H_4$-
c, R= 2-ClC_6H_4-
d, R= 4-ClC_6H_4-
e, R= 2-$NO_2C_6H_4$-
f, R= 2,4-di (NO_2)-6-BrC_6H_2-



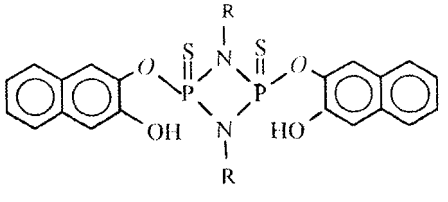
(Va-f) (X=Cl)



(Vg-l)



(VIa-f)



(VIg-l)

results that compound VIi was the most potent compound against gram positive and gram negative bacteria as well as filamentous fungi .

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