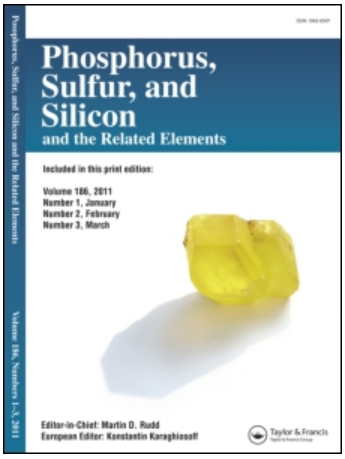

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF SOME NEW PYRIDYL DIARYLSULFIDE AND DIARYLSULFONES

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To cite this Article El-ezbawy, S. R. and Alshaikh, M. A.(1990) 'SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF SOME NEW PYRIDYL DIARYLSULFIDE AND DIARYLSULFONES', Phosphorus, Sulfur, and Silicon and the Related Elements, 48: 1, 111 — 116
To link to this Article: DOI: 10.1080/10426509008045887
URL: http://dx.doi.org/10.1080/10426509008045887

Phosphorus, Sulfur, and Silicon, 1990, Vol. 48, pp. 111–116
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SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF SOME NEW PYRIDYL DIARYLSULFIDE AND DIARYLSULFONES

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(Received February 22, 1989; in final form August 21, 1989)

Condensation of isonicotinaldehyde with 4-aminodiphenyl sulfides **I** and/or sulfones **II** gave 4-[*N*-[*p*-(diaryl/thio)]formimidoyl]-pyridine **III** and/or 4-[*N*-[*p*-(diarylsulfonyl)]-formimidoyl]pyridine **IV**. Cyclocondensation of mercaptoacetic acid on **III** and **IV** gave 3-[*p*-(diarylthio)]-2-(4-pyridyl)-4-thiazolidinones **V** and 3-[*p*-(diarylsulfonyl)]-2-(4-pyridyl)-4-thiazolidinones **VI** respectively. (Hetero/arylthio)-*N*-(6-methyl-2-pyridyl)-acetamides **VIII** have been synthesised via interaction of 6-methyl-2-chloroacetamido-pyridine **VII** with heterocyclic and/or aromatic mercaptans. Reaction of **VII** with piperidine and/or morpholine affords (**IX**). Biological activities of these compounds were tested.

Key words: Synthesis; antibacterial activity diarylsulfide and diarylsulfone; 4-thiazolidinones; pyridines.

The diverse pharmacological activities of pyridines[1–3] stimulated our interest for the synthesis of new derivatives of this ring system. It was of interest to incorporate pyridine nucleus into the well-known antibacterial fragments diarylsulfide, diarylsulfone and/or 4-thiazolidinone which have a wide application in the therapy of functional diseases.[4–9] Moreover molecular modification of the new combined molecule might lead to products of therapeutic significance.

In the present investigation different types of the hitherto unreported diarylsulfides and/or sulfones with heterocyclic moieties were prepared. 4-Aminodiaryl sulfides **I** and 4-aminodiaryl sulfones **II** were condensed with isonicotinaldehyde to give the corresponding 4-[*N*-[*p*-(diarylthio)]-formimidoyl]pyridine **III** and 4-[*N*-[(*p*-(diarylsulfonyl)]-formimidoyl]pyridine **IV**. Table I presents the data. IR spectra of **III** and **IV** showed a band at ~1580 cm^{-1} for C=N group. Products of the cyclocondensation reaction of **III** and/or **IV** with thioglycolic acid were identified as 3-[*p*-(diarylthio)]-2-(4-pyridyl)-4-thiazolidinones **V** and 3-[*p*-(diarylsulphonyl)]-2-(4-pyridyl)-4-thiazolidinones **VI** on the basis of their microanalytical data (Table II) and infrared spectra which showed bands at ~1740 cm^{-1} for

† Correspondence.

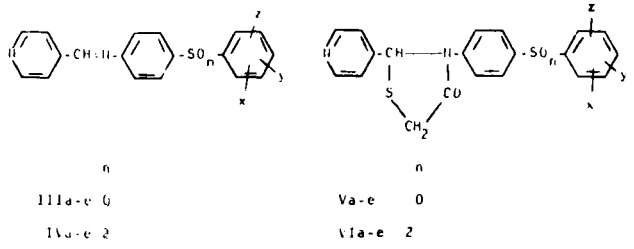
TABLE I

Physical data for compounds **III** and **IV**

Compd. no.	Crystn. solvent	X	Y	Z	m.p. °C	Yield %	Molecular formula	Anal.* calcd./found C	H	N
IIIa	EtOH	$2\text{-}NO_2$	$4\text{-}NO_2$	6-H	225	64	$C_{18}H_{12}N_4O_4S$	56.84	3.15	14.73
								56.79	3.16	14.51
IIIb	EtOH	$2\text{-}NO_2$	4-Br	6-H	156	42	$C_{18}H_{12}BrN_3O_2S$	52.17	2.89	10.14
								52.13	2.82	10.01
IIIc	EtOH	$2\text{-}NO_2$	4-Cl	6-H	176	61	$C_{18}H_{12}ClN_3O_2S$	58.46	3.24	11.36
								58.40	3.12	11.21
IIId	Me_2CO	$2\text{-}NO_2$	$4\text{-}CF_3$	$6\text{-}NO_2$	202	45	$C_{19}H_{11}F_3N_4O_4S$	50.89	2.45	12.49
								50.70	2.41	12.40
IIIe	$EtOH/H_2O$	$2\text{-}NO_2$	$4\text{-}NO_2$	5-F	119	69	$C_{18}H_{11}FN_4O_4S$	54.27	2.76	14.07
								54.21	2.69	14.05
IVa	CH_3CO_2H	$2\text{-}NO_2$	$4\text{-}NO_2$	6-H	179	36	$C_{18}H_{12}N_4O_6S$	52.43	2.91	13.59
								52.38	2.90	13.50
IVb	Me_2CO	$2\text{-}NO_2$	4-Br	6-H	279	50	$C_{18}H_{12}BrN_3O_4S$	48.43	2.69	9.42
								48.39	2.68	9.59
IVc	Me_2CO	$2\text{-}NO_2$	4-Cl	6-H	302	41	$C_{18}H_{12}ClN_3O_4S$	53.79	2.98	10.46
								53.63	2.98	10.41
IVd	EtOH	$2\text{-}NO_2$	$4\text{-}CF_3$	$6\text{-}NO_2$	280	69	$C_{19}H_{11}F_3N_4O_6S$	47.50	2.29	11.66
								47.41	2.28	11.60
IVe	EtOH	$2\text{-}NO_2$	$4\text{-}NO_2$	5-F	240	47	$C_{18}H_{11}FN_4O_6S$	50.23	2.55	13.06
								50.18	2.56	13.01

* Satisfactory analyses for S, Br and Cl were also obtained.

C=O, and compounds **VI** exhibited bands at ~1350 and ~1330 cm^{-1} for SO_2 group.



(For X, Y and Z, Tables I and II).

Furthermore, chloroacetylation of 6-methyl-2-amino-pyridine in dry benzene gave 6-methyl-2-chloroacetamidopyridine **VII** which was reacted with various heterocyclic or aromatic thiols to form (hetero/arylthio)-*N*-(6-methyl-2-pyridinyl)acetamides **VIII**. The structures of these compounds were established on the basis of their correct elemental analyses (Table III) and Ir spectral data which showed a band at ~3400 cm^{-1} for N–H, at ~1700 cm^{-1} assigned to secondary amide C=O. The NMR spectrum of 2-(2-benzthiazolylthio)-*N*-(6-methyl-2-pyridinyl) acetamide **VIIIc** showed resonances at δ: 2.3 (S, 3H, CH_3),

TABLE II

Physical data for compounds **V** and **VI**

Comp. no.	Crystn. solvent	X	Y	Z	M.P. °C	Yield %	Molecular formula	Anal.* calcd/found C	H	N
Va	EtOH/ether	2-NO_2	4-NO_2	6-H	133	71	$C_{20}H_{14}N_4O_5S_2$	52.86	3.08	12.33
								52.80	3.06	12.63
Vb	EtOH/ether	2-NO_2	4-Br	6-H	173	60	$C_{20}H_{14}BrN_3O_3S_2$	49.18	2.86	8.60
								49.10	2.83	8.51
Vc	C_6H_6	2-NO_2	4-Cl	6-H	144	75	$C_{20}H_{14}ClN_3O_3S_2$	54.11	3.15	9.47
								54.01	3.16	9.46
Vd	$CHCl_3$	2-NO_2	4-CF_3	6-NO_2	190	45	$C_{21}H_{13}F_3N_4O_5S_2$	48.28	2.49	10.72
								48.23	2.48	10.71
Ve	C_6H_6	2-NO_2	4-NO_2	5-F	161	55	$C_{20}H_{13}FN_4O_5S_2$	50.83	2.75	11.86
								50.61	2.73	11.81
VIa	EtOH/ether	2-NO_2	4-Br	6-H	215	50	$C_{20}H_{14}BrN_3O_5S_2$	46.15	2.69	8.07
								46.41	2.69	8.08
VIb	C_6H_6	2-NO_2	4-Cl	6-H	200 (decomp.)	66	$C_{20}H_{14}ClN_3O_5S_2$	50.47	2.94	8.83
								50.42	2.90	8.88
VIc	EtOH/ether	2-NO_2	4-CF_3	6-NO_2	210 (decomp.)	53	$C_{21}H_{13}F_3N_4O_7S_2$	45.56	2.35	10.12
								45.44	2.33	10.16

* Satisfactory analyses for S, Br and Cl were obtained.

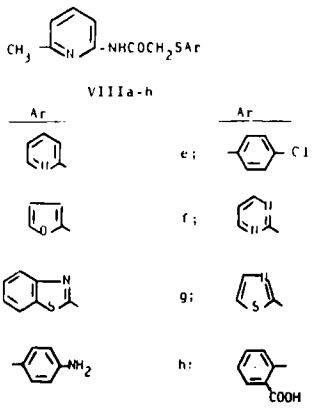
TABLE III

Physical data for compound **VIII**

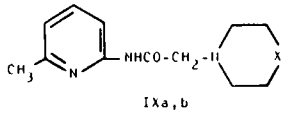
Comp. no.	Crystn. solvent	M.P. °C	Yield %	Molecular Formula	Anal.* Calcd./found C	H	N
VIIIa	EtOH	54	66	$C_{13}H_{13}N_3OS$	60.23	5.02	16.20
					60.19	5.01	16.34
VIIIb	Me_2CO	99	60	$C_{12}H_{12}N_2O_2S$	58.06	4.83	11.29
					58.28	4.89	11.11
VIIIc	EtOH	111	65	$C_{15}H_{13}N_3OS_2$	57.14	4.12	13.33
					57.09	4.01	13.20
VIIId	MeOH	66	38	$C_{14}H_{15}N_3OS$	61.54	5.49	15.39
					61.49	5.41	15.30
VIIIe	EtOH	55	50	$C_{14}H_{13}ClN_2OS$	57.44	4.44	9.57
					57.12	4.36	9.50
VIIIf	Me_2CO	159	39	$C_{12}H_{12}N_4OS$	55.38	4.62	21.52
					55.52	4.68	21.31
VIIIg	EtOH	134	48	$C_{11}H_{11}N_3OS$	49.81	4.15	15.85
					49.77	4.14	15.71
VIIIh	EtOH	260	50	$C_{15}H_{14}N_2O_3S$	59.60	4.64	9.27
					59.69	4.60	9.20

* Satisfactory analyses for S were also obtained.

4.3 (S, 2H, —CH_2—), 6.8–8.1 (m, 7H, aromatic 4 benzthiazole H and 3 pyridine H) and 10.1 ppm (S, 1H, NH—). The latter disappeared by D_2O treatment.



Many derivatives containing the aminoacylamide grouping are active as local anesthetics.[10,11] We therefore reacted **VII** with excess piperidine and morpholine to give **IXa,b** in moderate yield. The structures were established on the basis of their elemental analyses and Ir spectra.



IXa,b

where a) X = CH_2

b) X = O

Antimicrobial Activities

The antimicrobial activities of the prepared compounds against a variety of microbes were tested at concentration 0.1 Mg/ml in ethylene glycol by the paper disc technique.[12] These microorganisms include Gram positive and Gram negative bacteria. The bacteria used were: *Bacillus subtilis*, *Staphylococcus aureus*, *Esherichia coli*, and *Serratia marcescens*. Results showed that all tested compounds exhibited stronger activity on both the two first organisms than the latter ones. Table IV illustrates the data.

TABLE IV

Antibacterial activities of some selected compounds

Comp. no.	*Bacillus subtilis*	*Staphyloc. aureus*	*Escherich. coli*	*Serratia marcescens*
IIIa	+++	++	+++	++
IIIb	+++	++	+++	++
IIIc	++++	++	+	++
IVa	++++	+++	++	+++
IVb	+++	++	+	++
IVc	+++	+++	++	++
Vb	+	+	++	++
Vc	+	++	+	++
Vd	++++	++++	+	++
Ve	++	++	+	+
VIa	++	++	+	+
VIb	+++	++	++	++
VIc	+++	++	+	+
VIIIa	+++	+++	++	++
VIIId	++++	+++	++	+
VIIIh	++++	++++	+++	+

Strong effect (++++); medium effect (+++); fair effect (++); low effect (+).

EXPERIMENTAL

The time required for the completion of a reaction, and the purity of the products were determined by T.L.C. using solvent system: **I** = benzene–ethanol (4:1); **II** = benzene–ethanol (8:1); **III** = benzene–dioxan (7:3 v/v). Melting points are uncorrected. Ir spectra were obtained on a Perkin–Elmer 137B spectrophotometer using KBr Wafer technique. NMR-spectra were obtained in deuterated chloroform solutions with a Varian A-60 spectrometer.

4-[N-[p-(diarylthio)]formimidoyl]pyridine III and 4-[N-[(p-(diarylsulfonyl)]formimidoyl]pyridine **IV**. These were obtained by heating **I** and/or **II** (0.01 mole) with a slight excess of isonicotinaldehyde for $\frac{1}{2}$-1 hr., or by heating the reaction mixture in dimethyl sulphoxide for 1 hr. The reaction mixture was left overnight and treated with ethanol, filtered and purified by crystallization from the appropriate solvent, (Table I).

4-Thiazolidinones **V** *and* **VI**. A solution of **IV** and/or **V** (0.001 mole) and mercaptoacetic acid (0.001 mole) in dry benzene or dioxan (30 ml) was refluxed for 5–30 hr. water was removed by a Dean-Stark trap. Solvent was distilled off under reduced pressure and the product separated and purified (Table II).

6-Methyl-2-chloroactamidopyridine **VII**. To a well stirred, cooled, mixture of 2-amino-6-methyl pyridine (10.8 g, 0.1 mole) in dry benzene (50 ml), a solution of chloroacetyl chloride (11.3 g, 0.1 mole) in dry benzene (20 ml) was added dropwise during $\frac{1}{2}$ hr. The reaction mixture was stirred for

1 hr, and dissolved in Na_2CO_3 solution. The mixture was cooled and the product collected, washed with water and crystallized from ethanol, yield (9.2 g, 50%), m.p. 87–89°C.
Anal. Calc. for: $C_8H_9ClN_2O$; C, 52.03; H, 4.87; Cl, 19.24. Found; C, 52.10; H, 4.85; Cl, 19.39%.

(Hetero/arylthio)-N-(6-methyl-2-pyridyl)acetamides (**VIII**). Reaction of hetero and/or aryl mercaptan (0.002 mole) with alcoholic KOH (0.002 mole) gave the corresponding salt. This was added to **VII** (0.002 mole) in absolute ethanol (20 ml) and the mixture was refluxed for 5–37 hours, cooled and poured on ice-water. The precipitate was filtered off and recrystallized. In certain cases, the solvent was removed from the reaction mixture by vacuum distillation, the residue was washed with water and purified. Table III presents the data.

Reaction of 6-methyl-2-chloroacetamidopyridine with piperidine or morpholine. Compound **VII** (0.002 mole) was dissolved in dioxan (20 ml) and refluxed with excess of the amine (0.006 mole) for 4 hours. The amine hydrochloride was filtered off and the filtrate; cooled the precipitate was collected and crystallized from ethanol to give **IXa,b**; yields 68 and 55% m.p. 55–56°C and 65–67°C respectively.
Anal. Calcd. for **IXa**, $C_{13}H_{19}N_3O$: C, 66.95; H, 8.14; N, 18.03. Found: C, 66.90; H, 8.19; N, 18.17%.
Anal. Calcd. for **IXb**, $C_{12}H_{17}N_3O_2$: C, 61.80; H, 7.23; N, 17.86. Found: C, 61.35; H, 7.26; N, 17.68%.

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