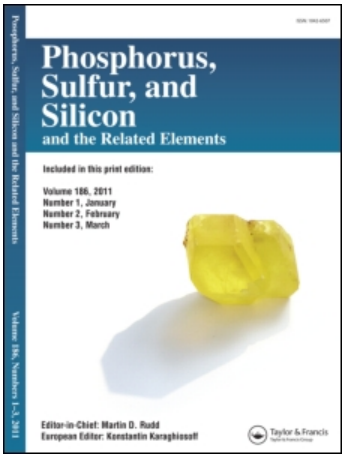

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SYNTHESIS OF S-(ARYL/HETERARYLOXAZOL-2-YL) [(ARYL / HETERARYLOXAZOL-2-YL)THIO]-ETHANETHIOATES AS POTENTIAL ANTIMICROBIAL AGENTS

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SYNTHESIS OF S-(ARYL / HETERARYLOXAZOL-2-YL)[(ARYL / HETERARYLOXAZOL-2-YL)THIO]-ETHANETHIOATES AS POTENTIAL ANTIMICROBIAL AGENTS

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The reaction of 2-mercaptoaryl/heteraryloxazoles with chloroacetylchloride in equimolar ratio afforded S-(aryl/heteraryloxazol-2-yl)chloroethanethioates (Ia–VIa) and also 1,2-bis-[(aryl/heteraryloxazol-2-yl)thio]-1-oxoethanes (Ib, IIc, IIIe, IVf, Vg and VIj) in 2 : 1 molar ratio in the basic medium. Treatment of (Ia–VIa) with different 2-mercaptoaryl/heteraryloxazoles in the presence of triethylamine yielded the corresponding S-(aryl/heteraryloxazol-2-yl) [(aryl/heteraryloxazol-2-yl)thio]ethanethioates (Ib–j–VIb–j). All the compounds have been characterized by elemental analyses, and spectral (IR, and PMR and Mass) data. The antimicrobial activity of some of the compounds has also been evaluated.

INTRODUCTION

The contact insecticidal activity of alkyl thiocyanates,[1] and significant biological properties of 2-alkylthiobenzthiazoles and 2-alkylthiobenzoxazoles[2] are associated with the sequence of atoms —S—C—N—. Motivated by these facts, we wish to present here the preparation of some hitherto unreported (S-(aryl/heteraryloxazol-2-yl)-[(aryl/heteraryloxazol-2-yl)thio]ethanethioates (Ib–j–VIb–j) with a view to evaluate their antimicrobial activity; as an extension of previous studies.[3,4]

RESULTS AND DISCUSSION

S-(Aryl/heteraryloxazol-2-yl)chloroethanethioates (Ia–VIa) were prepared by the interaction of appropriate 2-mercaptoaryl/heteraryloxazoles with chloroacetylchloride in equimolar ratio in the presence of methanolic KOH.

The structures of Ia–VIa were established by elemental analysis. The IR spectra exhibited the characteristic absorption bands[5] at 1680 ± 30 cm^{-1} for S—$\overset{O}{\overset{\|}{C}}$— in the

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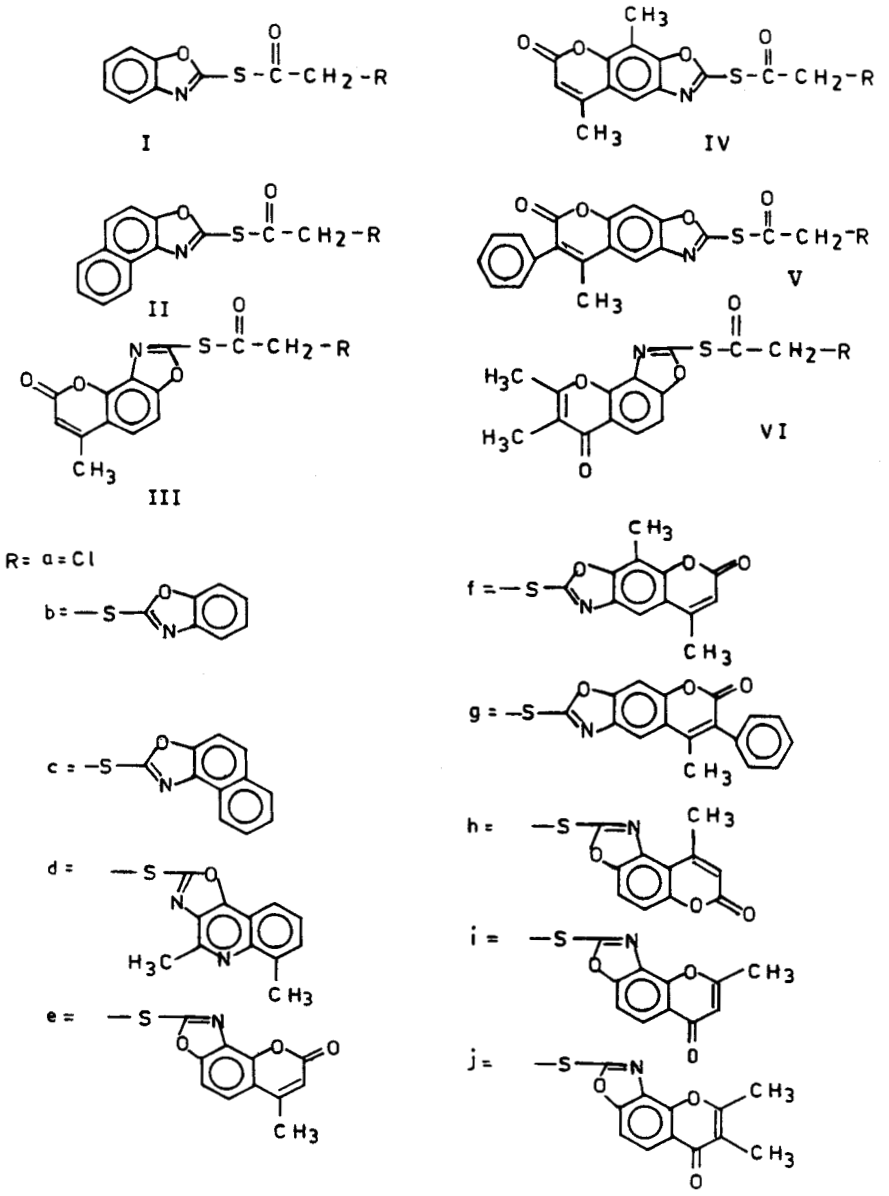

CHART 1

thiolesters. The PMR spectrum of IIIa in $CDCl_3$ (chemical shifts in δ-ppm down field from TMS as an internal reference) displayed a three protons singlet at δ 2.4 assignable to the 6-methyl group and a two protons singlet at δ 2.6 due to the methylene of the $-\overset{O}{\overset{\|}{C}}-CH_2-$ group. Because of the lactone carbonyl cone effect, the C_7 proton appeared as a singlet at δ 6.3. The two aromatic protons at C_4 and C_5 appeared at δ 7.4–7.6 as AB quartet (J = 10 Hz), which confirms the angular

TABLE I

Characterisation data of the compounds (I–VI)a–j

Compound+	M.P. °C	Yield (%)	Mol. formula.	Found* (%) (Calc) N	S
Ia	160	50	$C_9H_6NO_2SCl$	6.18 (6.15)	14.08 (14.06)
Ib	195	42	$C_{16}H_{10}N_2O_3S_2$	8.2 (8.19)	18.7 (18.71)
Ic	240	36	$C_{20}H_{12}N_2O_3S_2$	7.13 (7.14)	16.3 (16.32)
Id	292	42	$C_{21}H_{15}N_3O_3S_2$	9.96 (9.97)	15.21 (15.20)
Ie	270	35	$C_{20}H_{12}N_2O_5S_2$	6.61 (6.6)	15.07 (15.09)
If	256	38	$C_{21}H_{14}N_2O_5S_2$	6.38 (6.39)	14.6 (14.61)
Ig	265	36	$C_{26}H_{16}N_2O_5S_2$	5.58 (5.6)	12.7 (12.8)
Ih	283	32	$C_{20}H_{12}N_2O_5S_2$	(6.59 (6.6)	15.07 (15.09)
Ii	271	32	$C_{20}H_{12}N_2O_5S_2$	6.59 (6.6)	15.08 (15.09)
Ij	250	25	$C_{21}H_{14}N_2O_5S_2$	6.4 (6.39)	14.6 (14.61)
IIa	260	45	$C_{13}H_8NO_2SCl$	5.08 (5.04)	11.55 (11.53)
IIb	229	32	$C_{20}H_{12}N_2O_3S_2$	7.13 (7.14)	16.3 (16.32)
IIc	234	43	$C_{24}H_{14}N_2O_3S_2$	6.32 (6.33)	14.46 (14.48)
IId	242	38	$C_{25}H_{17}N_3O_3S_2$	8.91 (8.92)	13.6 (13.59)
IIe	215	36	$C_{24}H_{14}N_2O_5S_2$	5.88 (5.9)	13.58 (13.5)
IIf	215	36	$C_{25}H_{16}N_2O_5S_2$	5.70 (5.73)	13.12 (13.11)
IIg	254	35	$C_{30}H_{18}N_2O_5S_2$	5.08 (5.1)	11.62 (11.63)
IIh	262	36	$C_{24}H_{14}N_2O_5S_2$	5.88 (5.9)	13.51 (13.5)
IIi	180	38	$C_{24}H_{14}N_2O_5S_2$	5.91 (5.9)	13.46 (13.5)
IIj	160	38	$C_{25}H_{16}N_2O_5S_2$	5.72 (5.74)	13.12 (13.11)
IIIa	286	50	$C_{13}H_8NO_4SCl$	4.54 (4.52)	10.33 (10.34)
IIIb	272	30	$C_{20}H_{12}N_2O_5S_2$	6.58 (6.6)	15.07 (15.09)
IIIc	220	35	$C_{24}H_{14}N_2O_5S_2$	5.91 (5.9)	13.52 (13.5)
IIId	295	45	$C_{25}H_{17}N_3O_5S_2$	8.32 (8.35)	12.74 (12.72)
IIIe	280	60	$C_{24}H_{14}N_2O_7S_2$	5.52 (5.53)	12.66 (12.64)
IIIf	250	55	$C_{25}H_{16}N_2O_7S_2$	5.4 (5.38)	12.3 (12.31)
IIIg	313	48	$C_{30}H_{18}N_2O_7S_2$	4.83 (4.81)	11.1 (10.99)
IIIh	285	48	$C_{24}H_{14}N_2O_7S_2$	5.54 (5.53)	12.62 (12.64)
IIIi	258	25	$C_{24}H_{14}N_2O_7S_2$	5.51 (5.53)	12.63 (12.64)
IIIj	265	23	$C_{25}H_{16}N_2O_7S_2$	5.4 (5.38)	12.32 (12.3)
IVa	280	60	$C_{14}H_{10}NO_4SCl$	4.31 (4.32)	9.88 (9.89)

TABLE I (*Continued*)

Compound[+]	M.P. °C	Yield (%)	Mol. formula.	Found* (%) (Calc) N	S
IVb	310	40	$C_{21}H_{14}N_2O_5S_2$	6.38 (6.39)	14.63 (14.61)
IVc	240	48	$C_{25}H_{16}N_2O_5S_2$	5.72 (5.73)	13.14 (13.11)
IVd	320	35	$C_{26}H_{19}N_3O_5S_2$	8.11 (8.12)	12.4 (12.38)
IVe	272	37	$C_{25}H_{16}N_2O_7S_2$	5.4 (5.38)	12.32 (12.3)
IVf	325	50	$C_{26}H_{18}N_2O_7S_2$	5.22 (5.24)	11.96 (11.98)
IVg	280	35	$C_{31}H_{20}N_2O_7S_2$	4.67 (4.69)	10.74 (10.73)
IVh	295	36	$C_{25}H_{16}N_2O_7S_2$	5.39 (5.38)	12.32 (12.3)
IVi	255	38	$C_{25}H_{16}N_2O_7S_2$	5.36 (5.38)	12.31 (12.3)
IVj	245	36	$C_{26}H_{18}N_2O_7S_2$	5.23 (5.24)	11.97 (11.98)
Va	282	60	$C_{19}H_{12}NO_4SCl$	3.62 (3.63)	8.29 (8.3)
Vb	286	38	$C_{26}H_{16}N_2O_5S_2$	5.62 (5.6)	12.78 (12.8)
Vc	294	38	$C_{30}H_{18}N_2O_5S_2$	5.12 (5.1)	11.61 (11.63)
Vd	311	38	$C_{31}H_{21}N_3O_5S_2$	7.27 (7.25)	11.08 (11.05)
Ve	288	38	$C_{30}H_{18}N_2O_7S_2$	4.8 (4.81)	10.93 (10.99)
Vf	274	42	$C_{31}H_{20}N_2O_7S_2$	4.7 (4.69)	10.72 (10.74)
Vg	298	45	$C_{36}H_{22}N_2O_7S_2$	4.24 (4.25)	9.72 (9.73)
Vh	293	40	$C_{30}H_{18}N_2O_7S_2$	4.83 (4.81)	10.92 (10.99)
Vi	267	25	$C_{30}H_{18}N_2O_7S_2$	4.8 (4.81)	11.0 (10.99)
Vj	254	27	$C_{31}H_{20}N_2O_7S_2$	4.7 (4.69)	10.71 (10.74)
VIa	285	60	$C_{14}H_{10}NO_4SCl$	4.28 (4.3)	9.84 (9.83)
VIb	230	35	$C_{21}H_{14}N_2O_5S_2$	6.4 (6.39)	14.6 (14.61)
VIc	210	40	$C_{25}H_{16}N_2O_5S_2$	5.73 (5.74)	13.09 (13.11)
VId	270	43	$C_{26}H_{19}N_3O_5S_2$	8.11 (8.12)	12.39 (12.38)
VIe	276	50	$C_{25}H_{16}N_2O_7S_2$	5.4 (5.38)	12.32 (12.3)
VIf	238	38	$C_{26}H_{18}N_2O_7S_2$	5.23 (5.24)	11.97 (11.98)
VIg	247	32	$C_{31}H_{20}N_2O_7S_2$	4.7 (4.69)	10.72 (10.73)
VIh	280	32	$C_{25}H_{16}N_2O_7S_2$	5.37 (5.38)	12.28 (12.3)
VIi	262	25	$C_{25}H_{16}N_2O_7S_2$	5.36 (5.38)	12.31 (12.3)
VIj	278	44	$C_{26}H_{18}N_2O_7S_2$	5.23 (5.24)	12.00 (11.98)

[+] Solvents used for crystallisation were: Dioxane for IIIb–j, Vb–j; Ethanol for Ia–VIa, IVb–j; Methanol for Ib–j, IIb–j, VIb–j.

*All the compounds gave satisfactory C and H analyses.

structure of the compound. The mass spectrum of IIIa exhibited peaks m/z 309 (M^+; 3%), 233 (M^+—O=C=CHCl, 100), 207 (3,1), 206 (6.9), 205 (48), 204 (20.5), 172 (2.5), 151 (23), 106 (2.4), 91 (7), 77 (2), and 64 (7.1).

The reaction of Ia–VIa with various 2-mercaptoaryl/heteraryloxazoles in the presence of triethylamine resulted in the formation of the corresponding S-(aryl/heteraryloxazol-2-yl)[(aryl/heteraryloxazol-2-yl)thio]ethanethioates (Ib–j–VIb–j) Table I. But when 2-mercaptoaryl/heteraryloxazoles were treated with chloroacetyl chloride in 2 : 1 molar ratio in the presence of pyridine medium, the condensation took place simultaneously at both the ends of chloroacetylchloride in a single step giving rise to the respective 1,2-bis[(aryl/heteraryloxazol-2-yl)thio]-1-oxo-ethanes (Ib, IIc, IIIe, IVf, Vg and VIj); which were found to be identical (m.p., m.m.p., IR, CO-T LC) with those obtained by the two step procedure (vide supra).

IR spectra of Ib–j–VIb–j displayed characteristic absorption bands at 1320 ± 30 cm^{-1} for S—CH_2[6] and moreover, additional bands at 1560 ± 10, 1060 ± 10 and 1360 ± 10 cm^{-1} have also been found to be common, attributable to respective >C=N, —C—O—C— and >C—N= of the oxazole ring system.[7] PMR spectrum of Ib in $CDCl_3$ revealed a two protons singlet at δ 2.5 due to the $-\overset{O}{\overset{\|}{C}}-CH_2-$ group and eight aromatic protons appeared as a complex multiplet at δ 7.2–7.6. PMR ($CDCl_3$) data obtained from compound IIIb [δ 2.5 (2H, s, $-\overset{O}{\overset{\|}{C}}-CH_2$), δ 2.8 (3 H, s, $-CH_3$), δ 6.4 (1 H, s, C_7—H), δ 7.2–7.6 (6 H, m, Ar—H)] in agreement

TABLE II

Antimicrobial activity of the compounds (Ij, IId, IVc, e and g)

Compound	Antibacterial activity* Conc. µg/ml.	*E.Coli*	*S.lutea*	*B.megaterium*	*P.vulgaris*	*P.fluorescence*	Antifungal activity** Conc. µg/ml.	*C.Lunata*	*D.halodis*
Ij	250	—	—	0.5	—	—	360	0	0
	500	0.8	0.7	1.0	—	—	600	14.77	22.84
	800	1.3	1.3	2.0	—	0.5	840	23.08	30.32
IId	250	—	—	0.5	—	—	360	0	31.52
	500	0.5	—	1.0	—	0.5	600	86.00	100.00
	800	1.0	0.5	2.5	0.5	1.0	840	100.00	100.00
IVc	250	—	—	—	—	—	360	14.60	19.35
	500	0.5	0.5	0.8	—	—	600	37.31	40.47
	800	1.0	1.5	2.0	0.5	0.5	840	100.00	100.00
IVe	250	0.5	—	—	—	—	360	7.16	16.07
	500	1.0	2.0	1.0	—	—	600	14.77	25.00
	800	3.0	3.5	4.5	—	0.5	840	15.69	48.85
IVg	250	—	—	—	—	—	360	0	22.42
	500	0.5	1.0	—	0.5	—	600	6.43	27.27
	800	1.0	1.5	0.5	1.0	0.5	840	14.19	66.85

*Inhibition zone (in mm.)
**Percentage inhibition.

with the assigned structure. The mass spectra of Ib, IIIb and Vb exhibited molecular ion peaks at m/z 342, 424 and 500 respectively. These are also consistent with the observed fragmentation patterns.[8]

Antimicrobial activity

Compounds were tested against bacteria such as *Escheritia Coli*, *Sarcina lutea*, *Bacillus megaterium*, *Proteus vulgaris* and *Pseudomonas fluorescence* by using filter paper disc technique;[9] and against fungi,[10] such as *Curvularia lunata* and *Drechslera halodis*. Compounds Ij, IId, IVc, IVe and IVg showed very strong inhibition against *E.Coli*, *S.lutea* and *B.megaterium*, whereas IId, IVc and IVg showed moderate inhibition against *P.vulgaris* and *P.fluorescence* at the dose level of 800 μg/ml. Compounds IId and IVc showed 100% inhibition, while the compounds Ij, IVe and IVg showed 15–67% inhibition of spore germination in *C.lunata* and *D. halodis* at a concentration of 840 μg/ml (Table II)

EXPERIMENTAL

Melting points were taken in open glass capillaries and are uncorrected. Purity of all the compounds was routinely checked by TLC on silica gel G plates using iodine vapours as spray agent. IR spectra in KBr (ν_{max} in cm^{-1}) were recorded on Perkin-Elmer 337 grating instrument. PMR spectra in $CDCl_3$ were taken on Perkin-Elmer R-32 instrument at 90 MHz using TMS as an internal reference (chemical shifts in δ ppm and J values in Hz) and mass spectra on a JMS-D300 (Japan) mass spectrometer. 2-Mercapto-benzoxazole; 2-mercaptonaphth[1,2-d]oxazole;[11] 2-mercapto-6-methylpyrano[2,3-e]benzoxazole-8(H)-one; 2-mercapto-4,8-dimethylpyrano[3,2-f]benzoxazole-6(H)-one; 2-mercapto-8-methyl-7-phenylpyrano[3,2-f]benzoxazole-6(H)-one;[3] and 2-mercapto-7,8-dimethylpyrano[2,3-e]benzoxazol-6(H)-one[4] were prepared according to the reported methods.

2-mercapto-4,6-dimethyloxazolo[4,5-c]quinoline; 9-methylpyrano[3,2-e]benzoxazol-7(H)-one; and 8-methylpyrano[2,3-e]benzoxazole-6(H)-one were prepared from carbon disulphide and respective 3-amino-4-hydroxy-2,8-dimethylquinoline,[12] 5-amino-6-hydroxy-4-methylcoumarin[13] and 8-amino-7-hydroxy-2-methylchromone[14] following a similar procedure as reported earlier.[3]

Preparation of S-(aryl/heteraryloxazol-2-yl)chloroethanethioates (I–VI)a: General procedure. A mixture of 2-mercaptoaryl/heteraryloxazole (0.005 mol), chloroacetylchloride (0.005 mol) and potassium hydroxide (0.005 mol) was refluxed in methanol (20 ml) for 4 hrs. The reaction mixture was cooled and thus precipitated compound was filtered, washed with water, dried and recrystallised from suitable solvent to get the desired products (I–VI)a Table I.

Preparation of 1,2-bis[(aryl/heteraryloxazol-2-yl)thio]-1-oxoethanes (Ib, IIc, IIIe, IVf, Vg and VIj): General Procedure. To a solution of appropriate 2-mercaptoaryl/heteraryloxazole (0.011 mol) in methanol (20 ml) and pyridine (6 ml) was treated with chloroacetylchloride (0.005 mol) for 5 hrs. at 80–100°C. The reaction mixture was cooled, poured into ice-water, and neutralised with dilute HCl (10%) The separated solid was filtered, washed with water, dried and recrystallised from a proper solvent.

Preparation of S-(aryl/heteraryloxazol-2-yl)[(aryl/heteraryl-oxazol-2-yl)thio]ethanethioates (I–VI)b–j: General Procedure. The mixture of compound (I–VI)a (0.005 mol) and triethylamine (3 ml) in methanol (30 ml) was refluxed with the various 2-mercaptoaryl/heteraryloxazoles (0.005 mol) at 80–100°C for 3 hrs. The reaction mixture was cooled, poured into ice-water and neutralised with dilute HCl. The separated solid was filtered, washed with water, dried and recrystallised from an appropriate solvent to get the target compounds (I–VI)b–j (Table I).

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