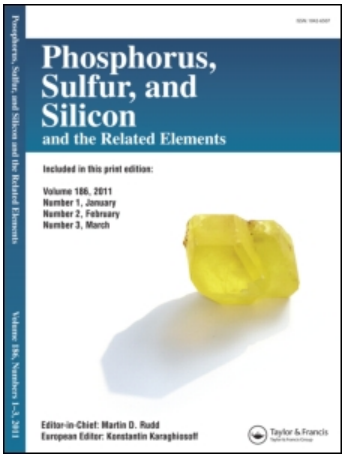

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BIOLOGICALLY ACTIVE THIONES DERIVED FROM PYRIDAZINONES

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Communication

BIOLOGICALLY ACTIVE THIONES DERIVED FROM PYRIDAZINONES

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A number of pyridazin-3-thione (**II**), some hydrazinopyridazine derivatives (**III**) and its Schiff base (**IV**) have been prepared. α-(3-thiopyridazinyl)-β-aroylpropionic acids (**VI**) have also been synthesised. Structural evidences are discussed. The antibacterial activity of these compounds has been studied.

The marked biological activities[1–5] possessed by pyridazinone derivatives and our work on pyridazinones and related compounds[6,7] tempted us to extend our study by exploring the antibacterial potential of some new pyridazinone derivatives bearing sulphur atom at position 3 of the molecule. In this investigation synthesis and antimicrobial activity of some thiopyridazinone derivatives are described.

6-(Substituted phenyl)-3(2H)-pyridazinone derivatives (**Ia–c**), the starting compounds, were treated with phosphorus pentasulphide in boiling xylene to furnish the corresponding 6-(substituted phenyl)3(2H)-pyridazine thione derivatives (**IIa–c**). The structure of **II** was inferred from analytical data.# The infrared spectra of thiones (**IIa–c**) exhibited bands at 1660 cm^{-1}, ν C = N, at the range 1380–1330 cm^{-1}, ν C = S and at the range 2160–2200 cm^{-1}, ν SH. Such IR data explain that the thiones (**IIa–c**) really exist in the thioamide (—NH—C=S) ⇌ iminothiol (—N=C—SH) dynamic equilibrium.

The behaviour of selected thione derivatives towards nitrogen nucleophiles is investigated.

Thus, condensation of **IIa** and **IIb** with hydrazine hydrate in boiling benzene gave the corresponding hydrazone derivatives (**IIIa**) and (**IIIb**) respectively. The infrared spectrum of **IIIa** showed bands at 1660 cm^{-1} (ν C=N) and at the region 3460–3440 cm^{-1} (ν NH). Structure of compounds (**III**) has been confirmed via unambiguous synthesis by interaction of **Ib** with hydrazine hydrate in boiling butanol and yielded **IIIb**.

The Schiff base (**IV**) has also been synthesized via condensation of (**IIb**) with benzylamine in boiling benzene. The infrared spectrum of (**IV**) showed well defined absorption bands attributable to ν C=N at 1655 cm^{-1} and ν NH at 3440 cm^{-1}.

The behaviour of β-aroylacrylic acids toward thiophenol has been investigated,[8] now we report in this paper the behaviour of β-(4-phenoxy)-; β-(3,4-dichloro)-; and β-(2-chloro-5-methyl)-benzoylacrylic acids (**Va–c**) toward pyridazinethione derivatives (**IIa–c**). The products are the α-thiopyridazino-β-(substituted; benzoylpropionic acids) (**VIa–f**). The structure of the sulphides (**VIa–f**) was confirmed

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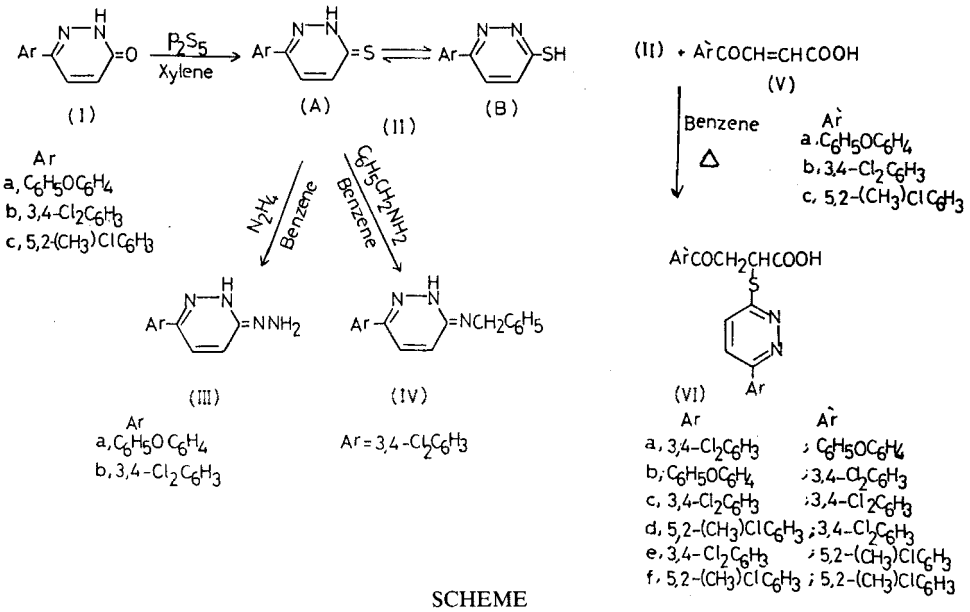

SCHEME

by: a) correct analytical data.* b) The infrared spectra revealed the presence of ν C=O (ketonic and acidic) at the region 1730, 1660 cm^{-1}, ν C=N at the range 1595–1590 cm^{-1} and ν OH at the region 3460–3420 cm^{-1}. Such IR data explain that, the thiopyridazinones (**IIa–c**) act as thiophenols which add to β-aroylacrylic acids (**Va–c**) to give α-carboxy-β-ketosulphides (**VIa–f**); the addition of the sulphur anion occurred α- to the carboxyl group in these instances, the polarization of the double bond by the keto group strongly outweighed that exhibited by the carboxyl group and so α-carbon atom accepted the nucleophiles more readily than β-carbon.

EXPERIMENTAL

Melting points are uncorrected. The infrared absorption spectra were determined with a Pye Unicam infrared spectrophotometer using KBr Wafer technique.

Reaction of β-aroyl acrylic acid with hydrazine hydrate: Formation of the corresponding pyridazinones (**Ia–c**). A hot solution of acids (0.01 mole) in ethanol, butanol and/or acetic acid (20 ml) was treated with hydrazine hydrate (0.01 mole). The reaction mixture was refluxed for 3 hrs and the products separated after cooling were crystallized from suitable solvents giving the corresponding pyridazinones (**Ia–c**).

Action of phosphorus pentasulphide on 6-aryl-3(2H)-pyridazin-3-ones (**Ia–c**)*: Formation of the pyridazin-3-thiones* (**IIa–c**).

General procedure. A mixture of **Ia–c** (0.01 mole) in 10 ml of xylene and (0.05 mole) of P_2S_5 was heated under reflux for 2 hrs, filtered while hot and left to cool. The product separated was crystallized from the suitable solvent as the thione derivatives (**IIa–c**) (Table I).

Action of hydrazine hydrate on **II***: Formation of hydrazinopyridazine derivatives* (**IIIa** and **IIIb**). A mixture of **IIa** or **IIb** (0.005 mole) and hydrazine hydrate (2 ml) in benzene (25 ml) was heated under reflux for 3 hrs. The solids obtained after concentration and cooling were recrystallized giving **IIIa** and **IIIb** respectively (Table I).

TABLE I

Characterization data of various compounds synthesized

Compd	M.p.°C Solvent of	Mol. formula	Found (%) / Calcd.			
			C	H	N	S
Ia	183	$C_{16}H_{12}O_2N_2$	72.88	4.67	10.55	-
	E		72.72	4.54	10.60	-
Ib	272	$C_{10}H_6ON_2Cl_2$	49.83	2.51	11.65	-
	E		49.79	2.48	11.61	-
Ic	142	$C_{11}H_9ON_2Cl$	59.67	3.99	12.57	-
	E		59.86	4.08	12.69	-
IIa	122	$C_{16}H_{12}ON_2S$	68.52	4.21	10.00	11.37
	E		68.57	4.28	10.0	11.42
IIb	215	$C_{10}H_6N_2Cl_2S$	64.77	2.41	10.89	12.50
	E		64.69	2.33	10.83	12.45
IIc	104	$C_{11}H_9N_2ClS$	55.88	3.87	11.85	13.50
	E		55.81	3.80	11.81	13.53
IIIa	174	$C_{16}H_{14}ON_4$	68.91	5.39	20.02	-
	T		69.06	5.32	20.14	-
IIIb	220	$C_{10}H_8N_4Cl_2$	47.12	3.17	22.00	-
	T		47.05	3.13	21.96	-
IV	255	$C_{17}H_{13}N_3Cl_2$	61.88	3.97	12.47	-
	E		61.81	3.93	12.72	-
VIa	137	$C_{26}H_{18}O_4Cl_2S$	59.49	3.43	5.31	6.19
	E		59.42	3.42	5.33	6.09
VIb	168	$C_{26}H_{18}O_4N_2Cl_2S$	59.41	3.47	5.13	6.11
	E		59.42	3.42	5.33	6.09
VIc	254	$C_{20}H_{12}O_3N_2Cl_4S$	47.58	2.42	9.15	6.40
	B		47.80	2.39	9.56	6.37
VId	153	$C_{21}H_{15}O_3N_2Cl_3S$	52.12	3.19	5.86	6.60
	E		52.26	3.11	5.81	6.64
VIe	152	$C_{21}H_{15}O_3N_2Cl_3S$	52.12	3.17	5.58	6.60
	E		52.26	3.11	5.81	6.64
VIf	118	$C_{22}H_{18}O_3N_2Cl_2S$	57.12	3.69	6.11	7.0
	E		57.26	3.90	6.07	6.94

// The elemental analysis shows satisfactory results for the halogen atoms.

E = Ethanol

T = Toluene

B = Benzene

TABLE II

Physical data of microbiological activities

Compd No	Nystatin (120 μ / ml) Saccharomyces cervisiae I.Z. (mn) 27.5	Neomycin (40 mg / ml) Bacillus pumilus I.Z. (mm) 203	Tetracyclin HCl (10 mg / ml) Micrococcus luteus I.Z. (mm) 26.7
Ia	•(-) ve	10.4	(-) ve
Ib	37.1	32.2	40.1
IIb	(-) ve	20.9	17.7
IIIa	(-) ve	11.8	19.9
IIIb	(-) ve	13.6	14.0
IV	12.8	12.7	(-)ve
VIa	13.5	34.5	13.7

• The negative control is zero

The inhibition zone as compared (mm) is 27.5, 20.3 and 26.7 respectively, and the diameter of empty inhibition zone (I.Z.) is 8.5 mm.

Interaction of **IIb** *with benzylamine: Formation of Schiff base* (**IV**). An equimolecular mixture of the thione derivative (**IIIb**) and benzylamine in 25 ml of benzene was refluxed for 3 hrs, to give the corresponding Schiff base (**IV**) as yellow flakes.

Reaction of β-aroyl acrylic acids (**Va–c**) *with the thione derivatives* (**IIa–c**)*: Formation of α-thiopyridazino-β-aroylpropionic acids* (**VIa–f**).

General procedure. A mixture of the thione derivative (**IIa–c**) in benzene (20 ml) and the appropriate β-aroylacrylic acid namely p-phenoxy-, 3,4-dichloro- and/or 2-chloro-5-methyl-β-benzoylacrylic acids (**Va–c**) in 20 ml of benzene and few drops of piperidine was heated on a steam bath for 3 hrs. The separated products were crystallized from a suitable solvent as α-thiopyridazino-β-aroylpropionic acids (**VIa–f**) (Table I).

Biological Activity. Compounds in this investigation were tested against different microorganisms namely, Saccharomyces cerevisiae, Bacillus pumilus and Micrococcus luteus comparing the effect with standard antibiotics such as Nystatin (120 u/ml), Neomycin (40 mg/ml) and Tetracycline hydrochloride (10 mg/ml), respectively. The biological tests were carried out on alcoholic extracts, by reported method,[9] the results obtained were tabulated (Table II).

The results show that compounds **Ib**, **IIb** and **VIa** exhibit a strong inhibition against Bacillus pumilus, and compounds **IIIa**, **IIIb**, **IV** a moderate inhibition. In the case of Saccharomyces cerevisiae, compound **Ib** shows a strong inhibition, compounds **IV** and **VIa** show a moderate inhibition, while compounds **Ia**, **IIb**, **IIIa** and **IIIb** are inactive. Compound **Ib** exhibits strong inhibition against Micrococcus luteus, while compounds **IIb**, **IIIa**, **IIIb** and **VI** exhibit moderate inhibition and compounds **Ia** and **IV** are inactive to the same organism. It is observed that compounds containing two chlorine atoms in the 3- and 4-positions augment the biological activity of the tested compound.

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