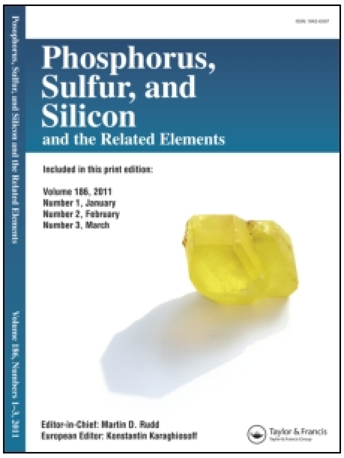

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STUDIES ON THE VILSMEIER-HAACK REACTION. PART XII: NOVEL HETEROCYCLO-SUBSTITUTED THIENO[2,3-c:5,4-c']DIPYRAZOLE DERIVATIVES

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STUDIES ON THE VILSMEIER-HAACK REACTION. PART XII: NOVEL HETEROCYCLO-SUBSTITUTED THIENO[2,3-c:5,4-c′]DIPYRAZOLE DERIVATIVES

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Only one 3-methyl group of 4,4′-bi-4H-pyrazole-5.5′(1H,1′H)-one (-thione) (**I**) has been found to undergo diformylation, chloro substitution of carbonyl group in the 5-position, and the cyclization of the 5-chloro-3-(2-amino-1-formylethenyl) derivative in one step to give the corresponding thieno[2,3-c:5,4-c′]dipyrazole (**III**). Also, compound 4,4′-bi-4H-pyrazole-5.5′(1H,1′H)-dithione (**II**) has been found diformylation of one 3-methyl group, and the cyclization of the 3-(2-amino-1-formylethenyl)-5.5′-dithiole derivative to give the same compound (**III**). Condensation of **III** with some secondary heterocyclic amines gave the aminomethylene derivatives (**V-VII**). However, the interaction of **III** with hydroxylamine, hydrazine hydrate and phenylhydrazine gave the corresponding isoxazolyl and pyrazolyl derivatives (**VIII-X**). Alkali hydrolysis of isoxazolyl compound gave cyanoaldehyde derivative **XII**. Novel heterocyclic compounds has been screened in vitro for studying their antibacterial and antifungal activities.

Key words: Pyrazolyl; isoxazolyl; piperidinyl; morpholinyl; piperazinyl-thieno[2,3-c:5,4-c′]dipyrazole; antimicrobial activity.

INTRODUCTION

Pyrazole derivatives are reported as pharmaceuticals for treatment of cerebrovascular disorders,[1] antiarrhythmic, sedative, platelet antiaggregating activities,[2–5] also, used as pesticides and fungicides.[6] Isoxazole derivatives were used as potential fungicides,[7] analogues of retinoids[8] and as adrenergic antagonists.[9] It has been reported that the replacement of carbonyl oxygen by sulphur atom in some heterocyclic compounds enhances their biological activity.[10–13] In continuation of our studies for the application of Vilsmeier reagent to some sulphur heterocyclic compounds and their biological activity, we describe herein the synthesis of some hitherto unreported of 4,4′-bi-4H-pyrazole-5.5′(1H,1′H)-one(-thione) (**I**) and/or 4,4′-bi-4H-pyrazole-5,5′(1H,1′H)-dithione (**II**) with several heterocyclic substituents at the 3-position in the hope to synthesize novel heterocyclic fused thienodipyrazole derivatives and to improve the physiological properties.

RESULTS AND DISCUSSION

Application of Vilsmeier reagent[14–19] on 3,3′-dimethyl-1,1′-diphenyl-4,4′-bi-4H-pyrazole-5-one-(1H,1′H)-5′-thione (**I**) in equal molar ratio on cold at 5–10°C for 3 hours afforded 4[5-chloro-3-(1-formyl-2-dimethylaminoethyenyl)-1-phenyl-4H-pyrazol-4-yl]-2,4-dihydro-5-methyl-2-phenyl-3H-pyrazol-3-thione (**Ia**), which revealed that reagent attacked only one methyl group and the other methyl group with the thio-carbonyl function still intact. However, when the reaction mixture of an equimolar ratio was carried out on hot at 70–75°C for 7 hours, a tricyclic fused compound 3-(1-formyl-2-dimethyl-aminoethenyl)-4-methyl-1,6-diphenyl thieno[2,3-c:5,4-c′]dipyrazole (**III**) was obtained. Furthermore, when the reaction mixture was carried in 2:1 molar ratio of Vilsmeier reagent and 4,4′-bi-pyrazole-5 one -5′-thione on cold at 5–10°C for 3 hours and/or on hot at 70°C gave the same cyclized compound (**III**). This indicates that the reaction proceeds via formylation of one 3-methyl group, chloro substitution of a carbonyl group followed by ring closure with elimination of HCl giving the corresponding fused thieno-compound (**III**). The structure was fully confirmed by the correct elemental analysis and the spectroscopic data (Tables I–III). IR spectrum showed the disappearance of absorption

TABLE I

Physico-chemical data of compound **I-VIII**

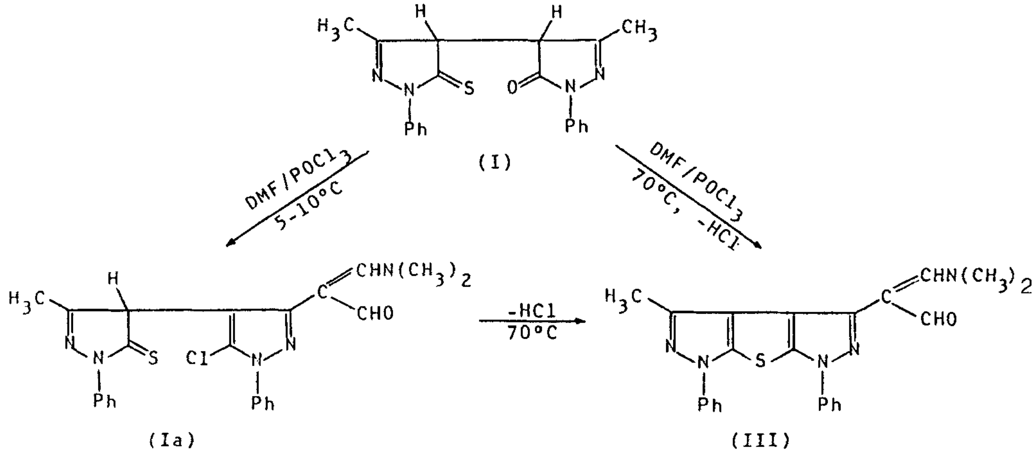
Compd.	m.p	Yield	Formula	Calculated 1%					Found 1%				
No.	°C	%	(M.W.)	C	H	N	S	Cl	C	H	N	S	Cl
I	191-2	85	$C_{20}H_{18}N_4OS$ (362.46)	66.28	5.01	15.46	8.85	-	66.31	5.00	15.79	8.75	-
II	150-2	87	$C_{20}H_{18}N_4S_2$ (378.52)	63.46	4.79	14.80	16.94	-	63.52	4.52	14.73	16.89	-
III	172	78	$C_{24}H_{21}N_5OS$ (427.53)	67.43	4.95	16.38	7.50	-	67.39	4.89	16.44	7.47	-
Ia	201	72	$C_{24}H_{22}N_5OSCl$ (463.99)	62.13	4.78	15.09	6.91	7.60	62.20	4.69	15.10	6.90	7.48
Ib	160	85	$C_{20}H_{17}N_4SCl$ (380.90)	63.07	4.50	14.71	8.42	9.31	63.10	4.46	14.69	8.50	9.26
IV	225	72	$C_{22}H_{16}N_4O_2S$ (400.46)	65.99	4.03	13.99	7.01	-	65.90	4.10	14.01	6.81	-
V	202	76	$C_{27}H_{25}N_5OS$ (467.60)	69.35	5.39	14.98	6.86	-	69.28	5.41	14.90	6.78	-
VI	225	68	$C_{26}H_{23}N_5O_2S$ (469.57)	66.51	4.94	14.91	6.83	-	66.47	5.01	14.87	6.90	-
VII	195-2	65	$C_{26}H_{24}N_6OS$ (468.58)	66.64	5.16	17.93	6.84	-	66.71	5.21	18.00	6.79	-
VIII	192	71	$C_{22}H_{15}N_5OS$ (397.46)	66.48	3.80	17.62	8.07	-	66.51	3.78	17.70	8.10	-
IX	240	62	$C_{22}H_{16}N_6S$ (396.48)	66.65	4.07	21.19	8.09	-	66.70	4.10	21.14	8.11	-
X	255	69	$C_{28}H_{20}N_6S$ (472.57)	71.16	4.26	17.78	6.78	-	71.20	4.21	17.82	6.81	-
XI	225	78	$C_{48}H_{38}N_{10}O_2S_2$ (851.03)	67.74	4.50	16.46	7.53	-	67.81	4.46	16.50	7.61	-
XII	163	66	$C_{22}H_{15}N_5OS$ (397.46)	66.48	3.80	17.62	8.07	-	66.51	3.76	17.70	8.11	-
XIII	198	68	$C_{22}H_{17}N_7S$ (411.49)	64.21	4.16	23.83	7.79	-	64.28	4.18	23.75	7.72	-
XIV	205	73	$C_{28}H_{21}N_7S$ (487.58)	68.97	4.34	20.11	6.57	-	69.01	4.40	20.06	6.60	-

TABLE II

IR spectra of some compounds in cm^{-1}

Assignment Compd. No.	$\nu >C=O$	$\nu >C=S$	α-β-Unsaturated ν CHO	Enolic ν OH malonaldehyde	ν C-Cl	ν C=C	Thieno- $\nu \diagdown_{S} \diagup$	ν CN	ν NH	ν NH_2	$\nu >C=N$	$\nu >C-CH_3$
I	1705	1320	-	-	-	-	-	-	-	-	1600	1400
II	-	1325	-	-	-	-	-	-	-	-	1600	1400
III	-	-	1625	-	-	1520	700	-	-	-	1595	1395
Ia	--	1320	1620	-	750	1500	-	-	-	-	1595	1395
IV	-	-	1625	3275	-	1515	695	-	-	-	1590	1400
V	-	-	1620	-	-	1520	690	-	-	-	1595	1395
VI	-	-	1620	-	-	1515	690	-	-	-	1600	1400
IX	-	-	-	-	-	1515	695	-	3285	-	1595	1400
XII	-	-	1625	-	-	1520	700	2285	-	-	1595	1395
XIII	-	-	-	-	-	1520	695	-	-	3310	1590	1395

band at 1710 cm^{-1} for $>C=O$ group presence enolic form and at 1565, 1255 cm^{-1} for $>C=S$ group. However, a new band appears at 1625 cm^{-1} for (acrolein-CHO group, vinylgous amide) Table II and the ^1H-NMR spectrum in TFA acid showed signals at δ2.22(s, 3H, CH_3 group), δ3.30(s, 6H of $-N(CH_3)_2$ group and at δ9.20(s, 1H, acrolein-CHO) Table III.



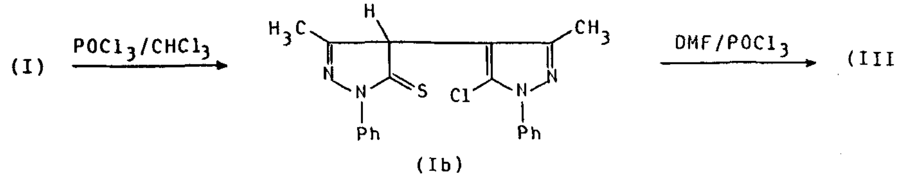
An alternative route for the confirmation of compound structure (**III**) by the conservation of 4,4′-bi-pyrazole-5-one-5′-thione (**I**) through the intermediate compound (**Ia**), then ring closure. It is quite clear that the action of $POCl_3$ in chloroform used 1:0.5 molar ratio of compound **I** and $POCl_3$ gave the corresponding 4-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-2,4-dihydro-5-methyl-2-phenyl-3H-

TABLE III

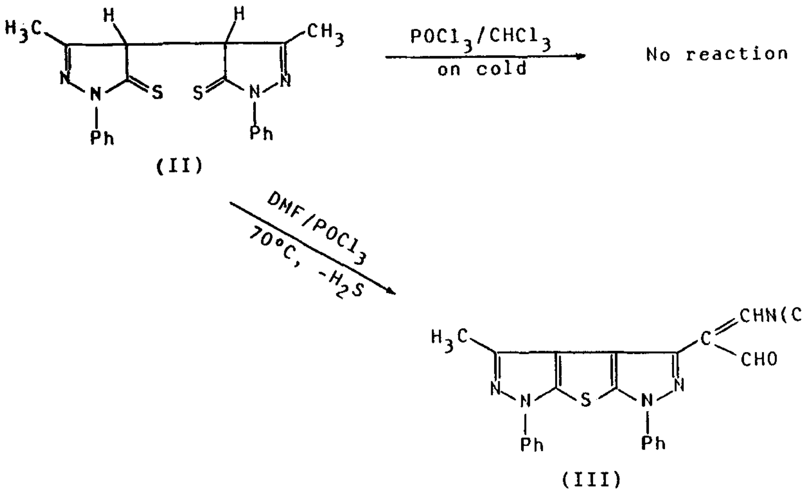
^{1}H-NMR spectra of some synthesized compounds (chemical shifts in δ ppm)

Compound No.	Aromatic protons (m)	$-N<^{CH_3}_{CH_3}$ (S)	$-CH_3$ (S)	α-β-Unsaturated CHO (S)	Enolic OH malonaldehyde (S)	Side-chain methine $=CH-N<$ (S)	$-N<^{CH_2-}_{CH_2-}$ (t)	$>NH$ (S)	NH_2 (S)
Ia	7.00-8.20(10 H)	2.82-2.92(6 H)	2.35(3 H)	9.15(1 H)	-	8.45(1 H)	-	-	-
III	7.15-8.35(10 H)	2.85-2.90(6 H)	2.40(3 H)	9.20(1 H)	-	8.50(1 H)	-	-	-
IV	7.20-8.15(10 H)	-	2.35(3 H)	9.25(1 H)	4.80(1 H)	8.35(1 H)	-	-	-
V	7.10-8.30(10 H)	-	2.38(3 H)	9.24(1 H)	-	8.45(1 H)	2.80(2t,4H,2 CH), 3.68(2t,4H,2 CH_2), 3.72(t,2H, CH_2).	-	-
VI	7.20-8.25(10 H)	-	2.33(3 H)	9.23(1 H)	-	8.44(1 H)	2.86(2t,4H,2 CH_2), 3.70(2t,4H,2 CH_2).	-	-
VII	7.22-8.30(10 H)	-	2.32(3 H)	9.25(1 H)	-	8.46(1 H)	2.84(2t,4H,2 CH_2), 3.70(2t,4H,2 CH_2).	9.85(1 H)	-
VIII	7.10-8.20(10 H)	-	2.36(3 H)	-	-	-	-	-	-
IX	7.15-8.20(10 H)	-	2.36(3 H)	-	-	-	-	10.60(1 H)	-
XII	7.10-8.25(10 H)	-	2.42(3 H)	-	5.00(1 H)	8.58(1 H)	-	-	-
XIII	6.80-8.45(15 H)	-	2.38(3 H)	-	-	8.52(1 H)	-	-	6.24(2 H)

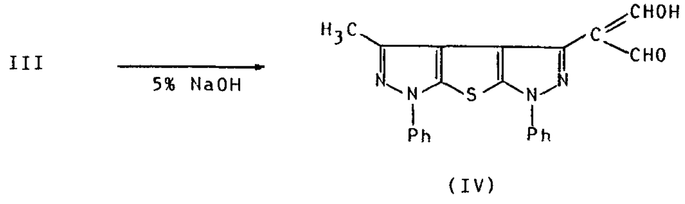
pyrazol-3-thione (**Ib**). On treatment of compound (**Ib**) by Vilsmeier reagent, simultaneously leads to the diformylation of one methyl group and ring closure giving the same cyclized thieno[2,3-c:4,5-c′]dipyrazole (**III**).



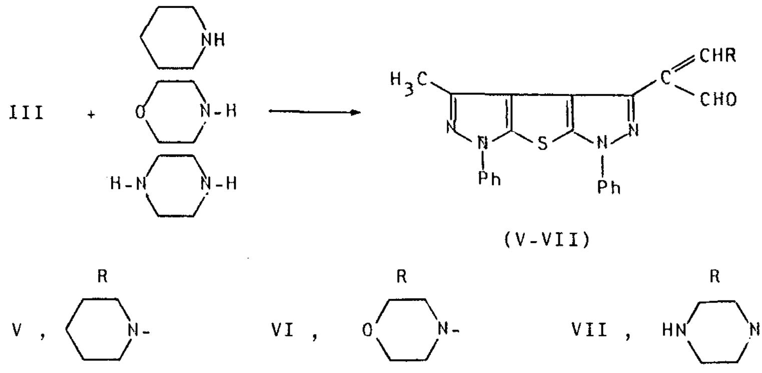
On the other hand, the action of $POCl_3$ in chloroform using 1:0.5 and/or 1:1 molar ratio on 3.3′-dimethyl-1,1′-diphenyl,4,4′-bi-4H-pyrazole-(1H,1′H)-5,5′-dithione (**II**) not reacted, but when using Vilsmeier reagent in molar ratio (usual conditions) afforded 3-(1-formyl-2-dimethylaminoethenyl)-4-methyl-1,6-diphenyl thieno[2,3-c:4,5-c′]dipyrazole (**III**), this means that the reaction proceeds via formylation of one 3-methyl group, followed by ring closure with elimination of hydrogen sulphide gas detect and giving the same cyclized thieno[2,3-c:4,5-c′]dipyrazole (**III**) according to the following scheme:



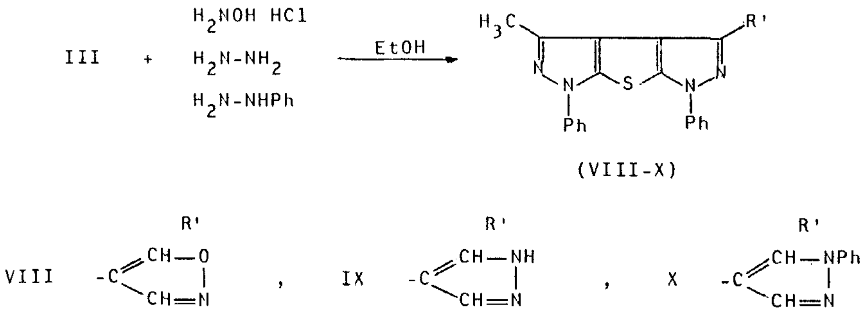
Thieno-dipyrazole derivative **III** was readily hydrolyzed by heating with 5% sodium hydroxide solution giving the corresponding malonaldehyde (**IV**) with evolution of dimethylamine, which give a pale yellowish brown coloration with iron (**III**) chloride due to the formation of enolic malonaldehyde group.



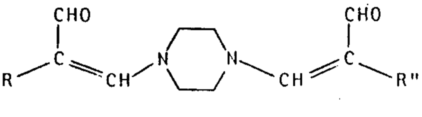
Furthermore, condensation of thieno-dipyrazole derivative **III** with some secondary heterocyclic amines such as piperidine, morpholine and piperazine in boiling absolute ethanol gave the expected aminomethylene derivatives (**V-VII**). The structures of these compounds were confirmed on the bases of the correct elemental analysis data (c.f. Table I). The IR spectra were in agreement with their structures indicating the presence of a sharp absorption band at 1625 cm^{-1} (side-chain CHO). ^1H-NMR spectrum of compound **V** in (TFA) CF_3COOH showed the presence of signals at δ3.72—2.86 (t. $>N\text{-}CH_2\text{-}$) due to the piperidine ring, besides signals due to the other protons (c.f. Table III).



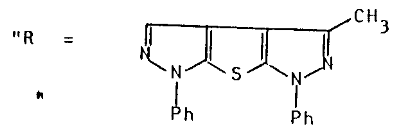
On the other hand, interaction of thieno-dipyrazole derivative **III** with hydroxylamine hydrochloride, hydrazine hydrate and phenylhydrazine afforded the corresponding 4-isoxazolyl, 4-pyrazolyl and 1-phenyl-4-pyrazolyl derivatives at the 3-position of thieno[2,3-c:5,4-c′]dipyrazole (**VIII-X**).



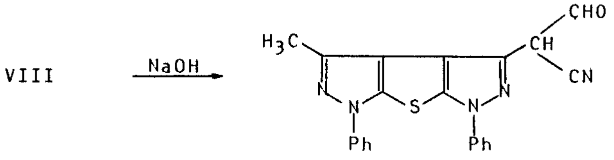
When piperazine was reacted with two moles of thieno-dipyrazole derivative **III** gave 1,4-piperazinediyl (**XI**) was obtained. IR, ^1H-NMR and microanalysis data of these compound were in accordance with the structural formula.



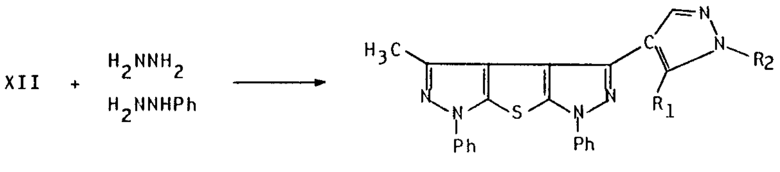
(XI)



On treatment isoxazole compound **(VIII)** with sodium hydroxide 2%, (20 ml) gave the cyanoaldehyde thieno-dipyrazole **(XII)** as shown by its solubility in alkali and the characteristic strong absorption band at 2285 cm^{-1} νC≡N and at 1625 cm^{-1} ν-CHO in their IR spectra.



(XII)



(XIII, XIV)

	R_1	R_2
XIII ,	H_2N	H
XIV ,	H_2N	Ph

Reaction of cyanoaldehyde derivative **(XII)** with hydrazine hydreate and/or phenylhydrazine in acetic acid gave the corresponding aminopyrazole derivatives **(XIII,XIV)**, as shown by their ready solubility in dilute hydrochloric acid and by their elemental analysis data. The IR spectra of these compounds were in agreement with the structures indicating the presence of a sharp -NH_2 band at 3310 cm^{-1}.

Antimicrobial Results

A. Antibacterial Activity

The results obtained from antibacterial activities showed that all synthesized compounds exhibit variable and pronounced activities (inhibition zones ranged from 10–180 mm) against a number of bacteria used (Table IV). It seems of interest to

TABLE IV

Antimicrobial screening of **I-XIV** compounds (inhibition zones in mm)

Compd.	Antibacterial activity						Antifungal activity		
No.	Staphylococcus aureus DSM 346	Bacillus cereus DSM 345	Serratia marcescens DSM 1608	Pseudomonas aeruginosa DSM 1299	Micrococcus luteus DSM 348	Klepsiella pneumoniae DSM 681	Altrnaria alternata Frier Keissler AUCC-1110	Penicillium chrysogenum Thom AUCC-530	Aspergillus flavus Link AUCC-164
I	-ve	30	40	30	80	50	30	90	-ve
II	-ve	-ve	-ve	60	100	85	50	95	60
Ia	105	50	110	85	120	130	85	90	65
III	140	30	130	105	145	150	75	115	80
Ib	88	50	90	75	90	110	60	85	70
IV	120	55	60	-ve	150	140	65	135	-ve
V	70	45	50	180	125	105	50	130	170
VI	50	60	-ve	-ve	50	145	-ve	10	20
VII	110	-ve	45	160	120	125	-ve	50	30
VIII	95	45	65	-ve	30	160	20	115	80
IX	35	20	135	140	95	90	-ve	95	85
X	120	70	125	130	110	140	70	140	120
XI	145	45	85	170	185	165	65	105	85
XII	150	90	115	160	190	185	105	130	115
XIII	45	20	105	110	65	85	-ve	30	90
XIV	110	85	105	115	90	105	85	130	110

DSM = Deutsche Sammlungvon Microorgamifman (German Collection of Microorganisms).

AUCC = Assiut University Culture Collection.

note that the prepared compounds are highly active (inhibition zones 30–185 mm) against *Micrococcus luteus* and *Klepsiella pneumoniae.* Whereas, piperidino-; *N*-phenyl pyrazolo-; pyrazolo- and di-piperazino- derivatives showed strong effects (inhibition zones 20–185 mm) against all bacteria used, and comparatively more active than the starting compounds **I** and **II**.

B. Antifungal Activity

From the antifungal screening, it was found that all synthesized compounds showed strong activities (inhibition zones ranged from 50–155 mm) against Penicillium chrysogenum, except compounds (8) whereas isoxazolyl; piperidino-; pyrazolyl; and dipiperazino- are highly active (inhibition zones from 80–170 mm) against fungi used (Table IV).

EXPERIMENTAL

All melting points were determined on a Kofler melting point apparatus and are uncorrected. IR spectra were recorded in KBr on a PYE-UNICAM SP3-100 Infrared Spectrophotometer (wavenumbers in cm^{-1}). ^{1}H-NMR spectra were recorded on a Varian EM 390-90 MHz NMR spectrometer using trifluoroacetic acid (TFA) as solvent and TMS as internal standard (chemical shifts in δ ppm). Elemental analysis was carried out by elemental analyser 240C.

3,3'-Dimethyl-1,1'-diphenyl-4,4'-bi-4H-pyrazole-5,5'(1H,1'H)-one-(-thione) (**I**): This compound was prepared according to the literature method.[1]

3,3'-Dimethyl-1,1'-diphenyl-4,4'-bi-4H-pyrazole-5,5'(1H,1'H)-dithione (**II**): A mixture of (3.5 g, 0.01 mole) of 3,3'-dimethyl-1,1'-diphenyl-4,4'-bi-4H-pyrazole-5,5'(1H,1'H)-dione, (1 g, 0.005 mole) of phosphorus penta sulphide and (3 ml) pyredine was refluxed for 4-6 hours at 60°C, then cooled, poured onto acedified crush ice with stirring for 2 hours, yellowish brown precipitate formed, filtered off, washed several times with cold water, dried, crystallized from water, given compound **II**.

3-(1-Formyl-2-dimethylaminoethenyl)-4-methyl-1,6-diphenyl thieno-[2,3-c:5,4-c']dipyrazole (**III**): To *N,N*-dimethylformamide (6 ml) cooled to 0°C, phosphoryl chloride (2.00 ml, 0.045 mole) was added and the mixture left to stand for 30 min. To this with stirring, bi-pyrazolone-(thione) **I** (0.025 mole) dissolved in *N,N*-dimethylformamide (7 ml) were added. The reaction mixture was left to stand for 10 min, then heated to 70°C for 8 hours with stirring, cooled, poured onto ice-cold water and treated with $NaHCO_3$ solution to pH 9. The reddish brown solid that separated out was filtered, washed with cold water and crystallized from ethanol to give compound **III**. Microanalysis data are given in Table I.

4[5-Chloro-3-(1-formyl-2-dimethylaminoethenyl)-1-phenyl-1'H-pyrazol-4'-yl]-2,4-dihydro-5-methyl-2-phenyl-3H-pyrazol-3-thione (**Ia**): To *N,N*-dimethylformamide (6 ml) cooled to 0°C, phosphoryl chloride (2.01 ml, 0.042 mole) was added and the mixture left to stand for 30 min. To this with stirring the bi-pyrazolone(-thione) **I** (0.02 mole) dissolved in *N,N*-dimethylformamide (5 ml) were added, the reaction mixture was left 2 hours with stirring, then poured into ice-water and treated with $NaHCO_3$ solution to give pale yellowish brown solid separated was filtered, washed thoroughly with cold water. The physical and chemical data are depicted in Table I.

4-(5-Chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-2,4-dihydro-5-methyl-2-phenyl-3H-pyrazol-3-thione (**Ib**): To chloroform (40 ml) solution of 4,4-bi-pyrazolone-(-thione) **I** (0.01 mole) cooled to 15°C, phosphoryl chloride (0.05 mole) was added dropwise with stirring for 3 hours at 40°C. A yellowish brown precipitate that separated was filtered, washed thoroughly with chloroform and crystallized from ethanol to give compound **Ib**.

3-(1-Formyl-2-hydroxyethenyl)-1,6-diphenyl-4-methyl-thieno[2,3-c:5,4-c']dipyrazole (**IV**): A mixture of aminoaldehyde derivative **III** (1 g) in 5% aq. NaOH (20 ml) was heated to 50°C till clear solution was obtained (30 min). It was cooled, filtered and acidified. The precipitate that separated was filtered, washed well with cold water and crystallized from ethanol. Their physical data are given in Table I.

3-[1-Formyl-2-(piperidinyl, morpholinyl and piperazinyl)-ethenyl]-4-methyl-1,6-diphenyl-thieno[2,3-c:5,4-c']dipyrazoles (**V-VII**): To a solution of **III** and/or **IV** (0.01 mole) taken in absolute ethanol (30 ml) was added an equimolar quantity of the heterocyclic amine and the mixture gently heated on a water bath for 1 hour. The solution was evaporated to dryness and the resulting residue poured onto ice-cold water was filtered, washed with cold water and crystallized from ethanol. The characterization of the compounds (**V-VII**) thus synthesized, are given in Table I.

3-(4-Isoxazolyl, 4-pyrazolyl, and 1-phenyl-4-pyrazolyl)-4-methyl-1,6-diphenyl-thieno[2,3-c:5,4-c']dipyrazoles (**VIII-X**): To a solution of compound **III** and/or **IV** (0.01 mole) in absolute ethanol (30 ml) was added an equimolar quantity of hydroxylamine hydrochloride, hydrazine hydrate and/or phenylhydrazine. The reaction mixture was refluxed for 2 hours, cooled, concentrated and poured onto water and crystallized from ethanol. Microanalytical data are listed in Table I.

Dimer formation (**XI**): To acrolein compound **III** (0.02 mole) in absolute ethanol (40 ml) was added (0.01 mole) quantity of piperazine and the mixture gently heated on a water bath. The solid that separated was filtered, washed with cold water and crystallized from ethanol. The data are given in Table I.

3-(1-Formyl-1-cyanomethyl)-1,6-diphenyl-4-methyl-thieno[2,3-c:5,4-c']dipyrazole (**XII**): The isoxa-zole compound **VIII** (1 g, 0.035 mole) taken in 5% aquoeus sodium hydroxide was heated till a clear solution was obtained (40 min). It was then cooled and acidified with hydrochloric acid. A yellowish brown solid that separated out was filtered, washed thoroughly with water and crystallized from aqueous ethanol. The physical and chemical data are listed in Table I.

3-(5-Amino-4-pyrazdyl and/or 5-amino-1-phenyl-4-pyrazolyl)-1,6-diphenyl-4-methyl-thieno[2,3-c:5,4-c']dipyrazole (**XIII, XIV**): A mixture of **XII** compound (1 g, 0.05 mole) and hydrazine hydrate (80%, 0.4 ml) and/or phenylydrazine (0.3 ml) taken in acetic acid (20 ml) was refluxed for 2 hours. The reaction mixture was concentrated, cooled and poured onto crushed ice. The aminopyrazoles **XIII** and aminophenyl pyrazole **XIV** compounds obtained as reddish brown solid separated out were filtered, washed thoroughly with water and crystallized from ethanol. Microanalytical data are presented in Table I.

Biological screening: The disc-diffusion method was used to measure the antimicrobial activity (Sleigh & Timbury, 1981).[20–22] The tested compound were dissolved in sterile dimethylformamide and added at a concentration of 0.5 mg/disk (Whatman No. 3 filter paper, 0.5 cm diameter). The antibacterial spectrum of the different compounds was tested with six strains of bacteria: *Staphylococcus aureus, Bacillus cereus, Serratia rhodnii, Pseudomonas aeruginosa, Micrococcus raseus* and *Klepsiella pneumoniae*. The antifungal effect of the same compounds was tested with five species of fungi: *Alternaria alternaria, Aspergillus flavus* and *Penicillium chrysogenum*. The culture medium for bacteria was nutrient agar (NA) (composed of beef extract, 3 gm, peptone 5 gm, agar, 15 gm/L and adjusted to pH 7 before sterilization at 121°C for 20 min). Glucose-Czapek's agar medium ($NaNO_3$, 2 gm; KH_2PO_4, 1 gm; $MgSO_4$, 0.5 gm; KCl, 0.5 gm; glucose, 10 gm; agar, 15 gm/L of distilled water) was used for fungi. The inoculated plates were incubated at 37 ± 1°C for 24–48 hours in case of bacteria and at 28°C for 7–8 days in case of fungi. The inhibition zones of microbial growth produced by different compounds were measured.

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