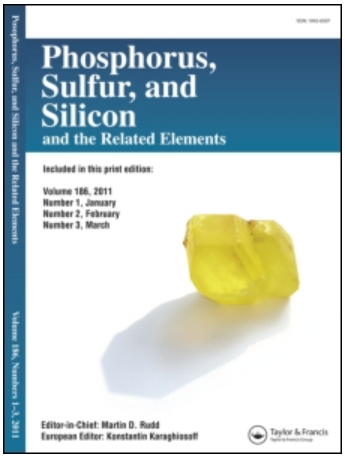

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SYNTHESIS AND REACTIONS OF SOME THIENO[2,3-d]PYRIMIDINE DERIVATIVES

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SYNTHESIS AND REACTIONS OF SOME THIENO[2,3-d]PYRIMIDINE DERIVATIVES

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5-Cyano-4-oxo-6-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine (**I**) reacts with P_2S_5 in pyridine to give pyrimidine-2,4-dithione (**II**). Further reaction of **II** with ethyl chloroacetate, chloroacetanilide, phenacyl bromide, bromoacetone and chloroacetonitrile gave the corresponding thieno[2,3-d]pyrimidine derivatives (**III–VI**). Interaction of compound $\mathbf{IV_a}$ with hydrazine hydrate in ethanol or diluted ethanol gave the hydrazide and hydrazino derivatives (**VII, IX**), which reacted with aromatic aldehydes to give the corresponding hydrazones ($\mathbf{VIII_{a-c}}$, $\mathbf{X_{a-c}}$). Alkaline hydrolysis of $\mathbf{IV_a}$ using KOH gave the acid **XI** with extrusion of thioglycolic acid.

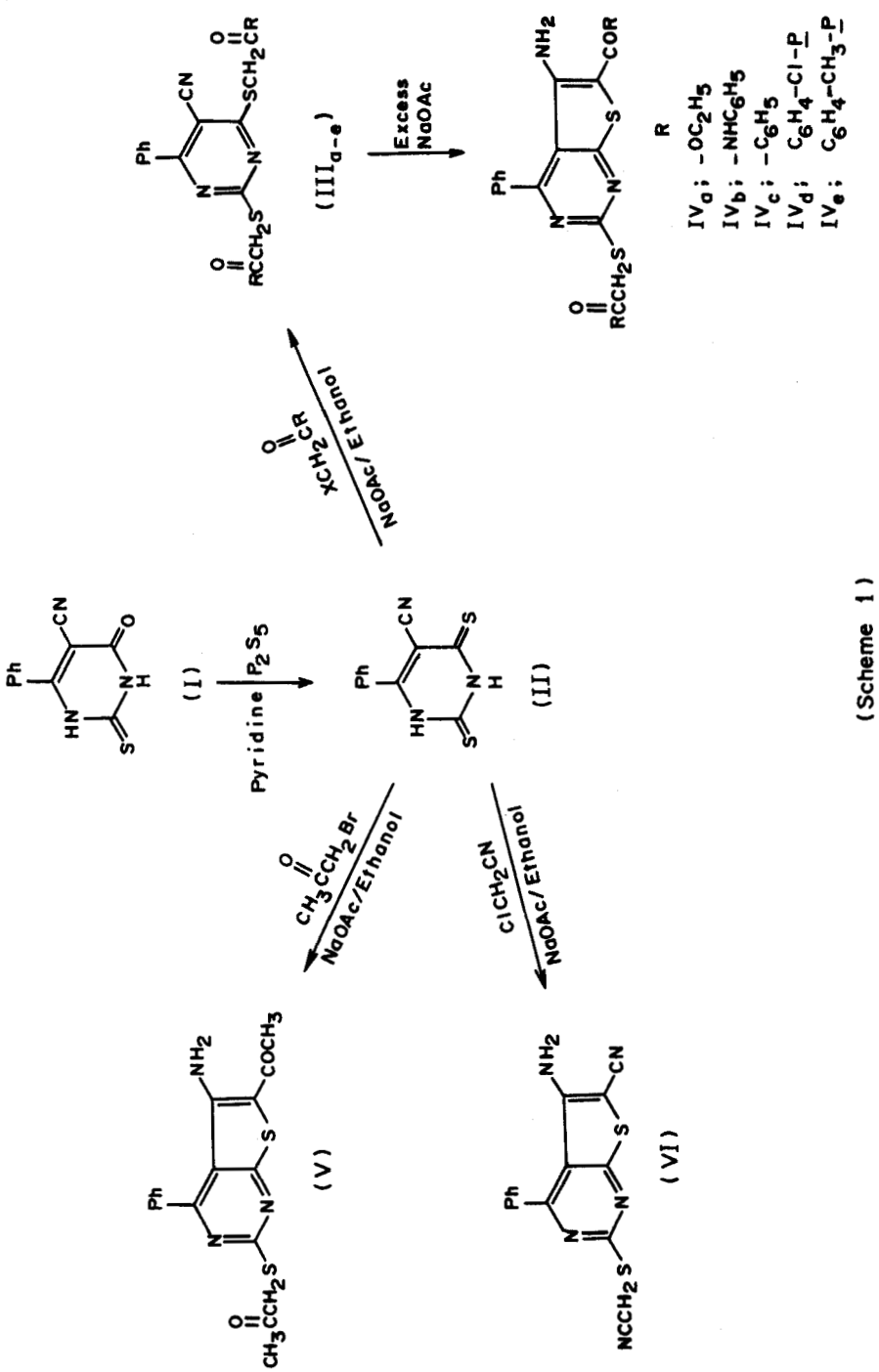
Key words: Pyrimidinedithione; thienopyrimidine; bactericidal activity.

In continuation of our work on the synthesis of biologically active heterocyclic compounds either as bioregulators, bactericides and/or fungicides[1,2] and also, for the medical uses of thieno[2,3-d]pyrimidine derivatives as platelet aggregation inhibitors[3] and their anti-convulsant activity,[4] the present work is aimed at the synthesis of dithiopyrimidine derivatives and thieno[2,3-d]pyrimidines to compare their biological activities with monothiopyrimidines that have been prepared previously.[1]

RESULTS AND DISCUSSION

The starting material for the synthesis of the desired compounds is 5-cyano-6-phenyl-1,2,3,4-tetrahydropyrimidin-2,4-dithione (**II**) which was synthesized by the reaction of the 4-oxo-derivative **I**[5] with P_2S_5 in refluxing pyridine. The dithio derivative (**II**)[7] reacts with ethyl chloroacetate, chloroacetanilide and phenacyl bromides in ethanol containing anhydrous sodium acetate to give the corresponding intermediates $\mathbf{III_{a-e}}$ which undergo ring closure in refluxing ethanol in the presence of excess anhydrous sodium acetate to give thieno[2,3-d]pyrimidines $\mathbf{IV_{a-e}}$. Also compound II reacts with two moles of bromoacetone or chloroacetonitrile in ethanol containing anhydrous sodium acetate to give directly the cyclised products **V** and **VI**. The I.R. spectra of the heterocycles $\mathbf{IV_a}$ showed two bands characteristic for two carbonyl groups, the first for the side chain carboxylate group at 1730 cm^{-1}, while the ring carboxylate group showed an absorption band at 1680 cm^{-1} due to the hydrogen bonding with the ortho amino group.[6] The reactions and results are illustrated in Scheme 1 and Table I.

Reaction of ethyl 5-amino-2-(ethoxycarbonylmethylthio)-4-phenylthieno[2,3-d]pyrimidinr-6-carboxylate ($\mathbf{IV_a}$) with hydrazine hydrate in ethanol gives the corresponding hydrazide derivative **VII** as hydrazine reacts only with the side chain ester group. This follows from the I.R. spectrum in which the band at 1730 cm^{-1}



(Scheme 1)

TABLE I

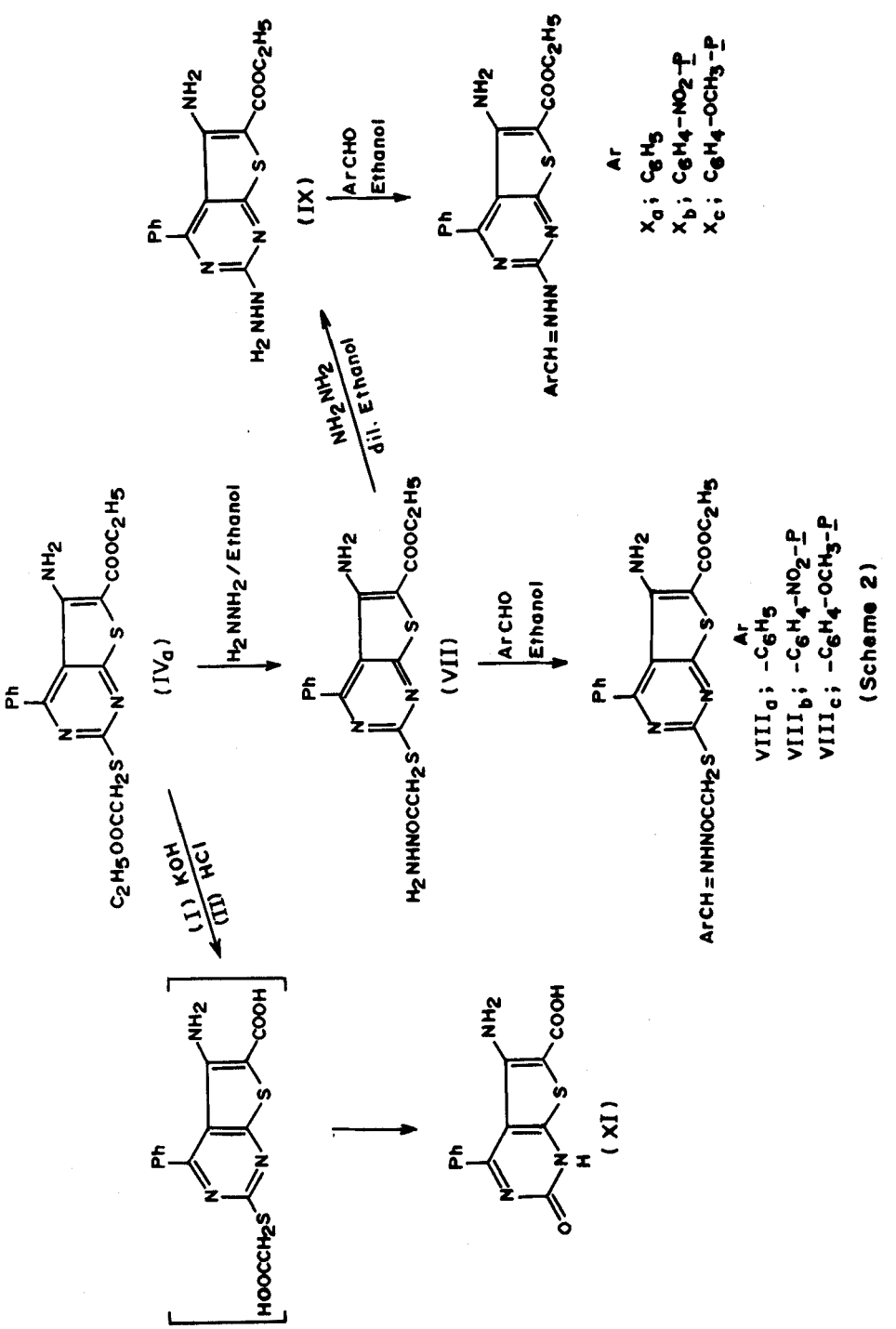
Physical and spectral data of compound (II–VI)

Compd.	MP[C]° (Solvent)	Yield % (colour)	Molecular[(a)] formula	I.R. cm^{-1}	^1H NMR δ	M.S M^+
II	328 (Dioxane)	65 (Orange)	$C_{11}H_7N_3S_2$	3180,3100(NH) 2240(CN),1220 (C=S).		
III_a	72 (Ethanol)	82 (Pale yellow)	$C_{19}H_{19}N_3O_4S_2$	2240(CN),1750 1730(C=0).		
III_b	235 (Acetic acid)	68 (White)	$C_{27}H_{21}N_5O_2S_2$	3360(NH),2220 (CN),1660(C=0)		
III_c	158 (Ethanol)	79 (Pale yellow)	$C_{27}H_{19}N_3O_2S_2$	2220(CN),1690 (C=0).		
III_d	203 (Ethanol)	76 (Pale yellow)	$C_{27}H_{18}ClN_3O_2S_2$	2240(CN),1680 (C=0).		
III_e	198 (Ethanol)	70 (White)	$C_{28}H_{21}N_3O_2S_2$	2220(CN),1680 (C=0).		
IV_a	137 (Ethanol)	77 (Yellow)	$C_{19}H_{19}N_3O_4S_2$	3500,3400(NH_2) 1680(C=0,ester ring), 1730(C=0 ester, side chain).	($CDCl_3$), 1.3(m,6H,$2CH_3$) 3.9(s,2H,CH_2), 4.3(m,4H $2CH_2$), 5.6(s,2H,NH_2), 7.4(s,5H, arom.).	417
IV_b	262 (Ethanol)	60 (Yellow)	$C_{27}H_{21}N_5O_2S_2$	3480,3380(NH_2) 3300(NH),1680, 1650(C=0).		

TABLE I (*Continued*)

Compd.	MP[C]° (Solvent)	Yield % (colour)	Molecular[(a)] formula	I.R. cm^{-1}	^1H NMR δ	M.S M^+
IV_c	170 (Ethanol	66 (Yellow)	$C_{27}H_{19}N_3O_2S_2$	3500,3400(NH_2), 1670(C=O).	($CDCl_3$), 4.6(s,2H,CH_2) 6.8(s,2H,NH_2), 7.4-8.0 (m,15H, arom.).	
IV_d	198 (Ethanol)	62 (Yellow)	$C_{27}H_{18}ClN_3O_2S_2$	3480,3370(NH_2), 1670(C=O).		
IV_e	335 (Ethanol)	56 (Yellow)	$C_{28}H_{21}N_3O_2S_2$	3420,3320(NH_2), 1660(C=O).		
V	185 (Ethanol)	76 (Orange)	$C_{17}H_{15}N_3O_2S_2$	3480,3360(NH_2), 1710,1660(C=O).	($CDCl_3$), 2.2(s,3H,CH_3) 2.4(s,3H,CH_3), 3.9(s, 2H,CH_2), 6.5(s,2H,NH_2), 7.4(s,5H, arom.).	357
VI	252 (Ethanol)	72 (Yellow)	$C_{15}H_9N_5S_2$	3460,3360(NH_2), 2260,2220(C=N).	(D_6MSO), 4.3(s,2H,CH_2), 5.9(s,2H,NH_2), 7.6 (s,5H, arom.).	

(a) All compounds give satisfactory microanalysis results C, ± 24%; H, ± 16%; N, ± 22%; S, ± 25%.



(Scheme 2)

TABLE II

Physical and spectral data of compounds (VII–XI)

Compd.	MP[C]° (Solvent)	Yield % (colour)	Molecular formula	I.R. cm^{-1}	^1H NMR δ	M.S M^+
VII	235 (Ethanol)	76 (Yellow)	$C_{17}H_{17}N_5O_3S_2$	3490,3380(NH_2), 3300($NHNH_2$), 1690,1670 (C=O).	(D_6MSO), 1.3(t,3H,CH_3), 3.8 (s,2H,CH_2), 4.2(m,4H,CH_2, NH_2 hydrazide), 5.9(s,2H,NH_2), 7.4(m,5H,arom)and 9.2(s,1H,NH).	
$VIII_a$	242 (Ethanol)	71 (Yellow)	$C_{24}H_{21}N_5O_3S_2$	3480,3380(NH_2), 3260(NH),1690, 1650(C=O).		
$VIII_b$	275 (Ethanol)	77 (Yellow)	$C_{24}H_{20}N_6O_5S_2$	3460,3360(NH_2), 3240(NH), 1690, 1650(C=O).		
$VIII_c$	230 (Ethanol)	68 (Yellow)	$C_{25}H_{23}N_5O_4S_2$	3480,3360(NH_2), 3240(NH),1680, 1660(C=O).		
IX	172 (Ethanol)	52 (Yellow)	$C_{15}H_{15}N_5O_2S$	3500,3400(NH_2), 3300($NHNH_2$), 1680(C=O).	($CDCl_3$), 1.3(t,3H,CH_3), 4.0 (s,2H,NH_2 hydrazino), 4.3 (q,2H,CH_2), 5.6(s,2H,NH_2), 6.7(s,1H,NH)and 7.5(s,5H,arom.).	329
X_a	253 (Ethanol)	72 (Yellow)	$C_{22}H_{19}N_5O_2S$	3500,3400(NH_2), 3360(NH), 1670 (C=O).		

X_b	284 (Acetic acid)	78 (Red)	$C_{22}H_{18}N_6O_4S$	3480,3380(NH_2), 3320(NH), 1670(C=O).
X_c	208 (Acetic acid)	68 (Orange)	$C_{23}H_{21}N_5O_3S$	3460,3360(NH_2), 3300(NH), 1670(C=O).
XI	195 (Acetic acid)	52 (Orange)	$C_{13}H_9N_3O_3S$	3500,3400(NH_2), 2700(OH acid), 1700, 1660(C=O).

for the —C— (side-chain) is shifted to 1690 cm^{-1} for the —C— hydrazide. The hydrazide derivative **VII** reacts easily with aromatic aldehydes in ethanol to give the corresponding hydrazone derivatives $\mathbf{VIII_{a-c}}$. Alternatively the hydrazide compound reacts with an excess of hydrazine hydrate in ethanol/H_2O (6:4) to give ethyl 5-amino-2-hydrazino-4-phenylthieno[2,3-d]pyrimidine-6-carboxylate (**IX**) as a result of extrusion of a molecule of thioacetic acid hydrazide. The hydrazino derivative reacts with aromatic aldehydes in ethanol to give the corresponding hydrazones $\mathbf{X_{a-c}}$. Hydrolysis of ($\mathbf{IV_a}$) with 10% KOH gave 5-amino-2-hydroxy-4-phenylthieno[2,3-d]pyrimidine-6-carboxylic acid (**XI**) by removal of the thioglycolic acid side chain. The results are given in Scheme 2 and Table II.

EXPERIMENTAL

All melting points are uncorrected and were determined on an electric melting point apparatus (Gallen Kamp. I.R. spectra were determined with a Pye-Unicam infrared spectrophotometer using KBr Wafer technique. ^1H NMR spectra were recorded on a 90 MHZ Varian NMR spectrometer in the suitable deuterated solvent using TMS as internal standard. Mass spectra were determined on Dupont 21-292 B mass spectrometer at an ionizing potential of 75 ev, ionizing current 30 μA, source temperature 200°C.

5-Cyano-6-phenyl-1,2,3,4-tetrahydropyrimidine-2,4-dithione (**II**). A mixture of **I**[5] (0.01 mol) and P_2S_5 (0.01 mol) in dry pyridine (30 ml) was refluxed for 5 hours, after which it was poured into ice/water mixture. The precipitated product thus formed was collected by filtration and washed several times with water.

Reaction of **II** *with ethyl chloroacetate, chloracetanilide and phenacyl bromides* ($\mathbf{III_{a-e}}$).

General procedure. A mixture of **II** (0.01 mol) and haloesters or haloketones (0.02 mol) was refluxed in ethanol (30 ml) for 1 hour in the presence of anhydrous sodium acetate (2 g). The reaction mixture was concentrated, cooled and the precipitated products were collected by filtration and crystallised from suitable solvents. The results are listed in Table I.

Cyclization of compounds ($\mathbf{III_{a-e}}$).

General procedure. To a solution of $\mathbf{III_{a-e}}$ (0.01 mol) in ethanol (50 ml), anhydrous sodium acetate (5 g) was added, the mixture was refluxed for 5 hours, then cooled and the precipitated products IVa–e were collected by filtration, washed with water and crystallised from suitable solvents. The results are listed in Table I.

Synthesis of 6-acetyl-2-acetylmethylthio-5-amino-4-phenylthieno-[2,3-d]pyrimidine (**V**) *and 5-amino-6-cyano-2-cyanomethylthio-4-phenylthieno[2,3-d]pyrimidine* (**VI**).

General procedure. A mixture of **II** (0.01 mol) and bromoacetone or chloroacetonitrile (0.02 mol) was refluxed in ethanol (50 ml) in the presence of anhydrous sodium acetate (5 g) for 6 hours. The precipitated products thus formed were collected while hot by filtration, washed with water and crystallised from suitable solvents. The results are given in Table (I).

Synthesis of ethyl 2-(hydrazinocarbonyl-methylthio)-5-amino-4-phenylthieno[2,3-d]pyrimidine-6-carboxylate (**VII**). A mixture of $\mathbf{IV_a}$ (0.01 mol) and hydrazine hydrate (0.01 mol) in ethanol (50 ml) was refluxed for 15 minutes. The precipitated product which formed was filtered off while hot, washed several times with ethanol and air dried.

Synthesis of ethyl-5-amino-2-arylidine hydrazino carbonyl methylthio-4-phenylthieno[2,3-d]pyrimidine-6-carboxylate ($\mathbf{VIII_{a-c}}$). A mixture of the hydrazide derivative **VII** (0.01 mol) and the aromatic aldehyde (0.01 mol) in ethanol (30 ml) was refluxed for 30 minutes, then cooled and the solid products were collected by filtration.

Synthesis of ethyl-5-amino-2-hydrazino-4-phenylthieno[2,3-d]pyrimidine-6-carboxylate (**IX**). To a solution of **VII** (0.01 mol) in ethanol/H_2O (6:4) (50 ml), hydrazine hydrate (0.04 mol) was added. The mixture was heated under reflux on a water bath until the odor of hydrogen sulfide ceased. The reaction mixture was then concentrated, and the precipitate which formed after cooling was collected by filtration, washed several times with cold ethanol and air dried.

Synthesis of ethyl-5-amino-2-arylidenehydrazino-4-phenylthieno[2,3-d]pyrimidine-6-carboxylate ($\mathbf{X_{a-c}}$). A mixture of the hydrazino derivative **IX** (0.01 mol) and the aromatic aldehyde (0.01 mol) was refluxed in ethanol (30 ml) for 30 minutes. The precipitated products which formed were collected while hot by filtration.

Synthesis of ethyl-5-amino-6-carboxy-4-phenylthieno[2,3-d]pyrimidin-2(1H)one (**XI**). A mixture of $\mathbf{IV_a}$ (0.01 mol) and alcoholic potassium hydroxide 10% (40 ml) was heated under reflux for 2 hours. The potassium salt thus formed was collected by filtration, dissolved in water (30 ml) and acidified with dilute hydrochloric acid. The solid product was filtered off, washed several times with water and dried in the air. The results are given in Table II.

Biological Activity. Bactericidal activity of the newly synthesized compounds has been tested against two pathogenic gram positive bacteria *Staphylococcus* and *Bacillus cereus*, and two other gram negative bacteria *Serratia sp*. and *Klebsiella sp*. The biological activity, as expressed by the growth of the inhibition zones of the tested microorganism, showed that dithiopyrimidine (**II**) is active against *S. coccus* (16 mm) and *Serratia sp*. (14 mm). The diester derivative $\mathbf{III_a}$ has less activity with the same organisms (11 mm) and (10 mm) respectively, compound **VI** is active against *Serratia sp*. (15 m). The hydrazino derivative **IX** is active against *S. coccus* (11 mm). The rest of synthesised compounds showed no effect on any of the microorganism tested.

Three fungal species, used in the present investigation were *Penicillium nigricans, Aspergillus flavus* and *Aspergillus fumigatus*. The newly synthesized compounds showed no activity against any of the fungi tested except compound $\mathbf{X_a}$ which showed moderate activity against *Aspergillus flavus* (10 mm).

Conclusion. From the above results it is quite clear that monothiopyrimidine derivatives are more potent than dithiopyrimidines as bactericides and/or fungicides. Fusion of a thiophene moiety to the pyrimidine nucleus has no significant effect on the activity.

REFERENCES

1. Z. H. Khalil, A. A. Abdel Hafez and A. A. Ahmed, *Phosphorus Sulfur and Silicon*, **45,** 81 (1989).
2. Z. H. Khalil, A. S. Yanni, A. A. Khalaf, A. A. Abdel Hafez and R. F. Abdo, *Bull. Chem. Soc. Jpn.*, **61,** 1345 (1988).
3. L. Siegfried, G. Micheal, W. Guenter, C. Erika, L. Dieter and L. Guenter, Ger. Pat., D 236, 096; C.A., **105,** 226639 (1986).
4. A. P. Mkrtchyan, S. G. Kazaryan, A. S. Noravyan, R. A. Akopyan, I. A. Dzhagatspanyan, N. E. Akopyan and A. G. Akopyan, *Khim. Farm. Zh.*, **20,** 1312 (1986); C.A. **106,** 168814z (1987).
5. S. Kambe, K. Saito and H. Kishi, *Synthesis*, **4,** 287 (1979).
6. F. J. Guodrado, M. A. Perez and J. L. Soto, *J. Chem. Soc. Perkin Trans.*, **I,** 2447 (1984).
7. N. S. Ibrahim, M. H. Mohamed and M. H. Elnagdi, *Chem. Ind. (London)*, **8,** 270 (1988).