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Synthesis and Biological Studies of Bis-Heterocycles

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Reaction of succinic acid hydrazide with substituted isothiocyanate gave corresponding thiosemicarbazides (IIa–c) in good yields. The acid catalysed cyclodehydration of (IIa) gave corresponding oxadiazole (Va). The base catalysed cyclodehydration of (IIa–c) gave respective bis-triazoles (IIIa–c) and cylisation of (IIa–c) with 99% hydrazine hydrate gave respective N-amino triazoles (VIa–c). Reaction of oxalic acid hydrazide with CS_2/KOH gave the corresponding salt (VI). Cyclisation of (VI) with hyrazine hydrate and phenyl hydrazine hydrate gave corresponding 4-substituted bis-triazoles (VIIa–b). Treatment of (VI) with CH_3I/CH_3OH gave the methyl salt (VIII). Prolonged refluxing of (VI) with KOH/C_2H_5OH gave bis-5-mercapto-1,2,4-oxadiazole (IX).Treatment of substituted benzoic acid with acid hydrazide in presence of $POCl_3$ yielded 5-substituted oxadiazole (Xa–b). Sample number Xa–b on cyclisation with hydrazine hydrate and phenyl hydrazine hydrate gave (XIa–d). Potassium salt (VI) on treating with substituted aniline gave (XIIa–b). All the above compounds are screened for antimicrobial and anthelmintic activities. They showed moderate to high activity.

INTRODUCTION

Compounds containing triazole and thiadiazole ring are known to possess fungicidal[1,2], pesticidal[3], insecticidal[4], bactericidal[5,6] and anti-inflammatory[7] activities. Some bis-heterocycles[8] have recently been reported to display fungicidal, antiviral against HIV, anticancer and antifertility[9] activity.

We now report the synthesis of various bis-1,2,4-triazoles, bis-1,3,4-thiadiazole and bis-1,3,4-oxadiazoles.

The succinyl hydrazide (I) reacted with *p*-chlorophenyl, methyl and allyl isothiocyanates to yield thiosemicarbazides (IIa–c) in quantitative yields.

The acid catalysed cyclodehydration of thiosemicarbazide (IIa) using anhydrous orthophosphoric acid gave 1,2-bis-(5-*p*-chlorophenylamino-1,3,4-thiadiazole) ethanes (Va).

The base catalysed cyclodehydration of (IIa–c) using 4% aqueous sodium hydroxide gave the respective 1, 2-bis-(4-*p*-chlorophenyl-5-mercapto-1,2,4-triazole) ethanes (IIIa), 1,2-bis-(4-methyl-5-mecrapto-1,2,4-triazole) ethanes (IIIb) and 1,2-bis-(4-allyl-5-mercapto-1,2,4-triazole) ethanes (IIIc) respectively.

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The cyclisation of (IIa–c) using 99% hydrazine hydrate gave 1,2-bis-(4-amino-5-*p*-chlorophenylamino-1,2,4-triazole) ethanes (IVa), 1,2-bis-(4-amino-5-methyl-amino-1,2,4-triazole) ethanes (IVb) and 1,2-bis-(4-amino-5-allylamino-1,2,4-triazole) ethanes (IVc) respectively.

The oxalyl hydrazide reacted with CS_2/KOH (alcoholic) and gave the potassium salt (VI). The cyclisation of salt (VI) with substituted amines yields bis-(4-amino-substituted-5-mercapto-1,2,4-triazoles) (VIIa–b). Cyclisation of VI with KOH/C_2H_5OH for 18 h. and CH_3I/CH_3OH gave bis-(5-mercapto-1,2,4-oxadiazole) (IX) and methyl salt (VIII) respectively.

Oxalyl hydrazide undergoes cyclisation with substituted benzoic acids in $POCl_3$ to give bis-(5-benzoic acid substituted 1,2,4-oxadiazole) (Xa–b). Further treatment of Xa–b with R_1—NH_2 gives bis-(4-amino substituted 5-benzoic acid substituted 1,2,4-triazoles) (XIa–d). Potassium salt (VI) on cyclisation with substituted aniline gave bis-(4-anilino substituted-5-mercapto-1,2,4-triazole).

EXPERIMENTAL AND DISCUSSION

Melting points were determined in open capillaries and are uncorrected. The IR spectra were recorded in nujol on a Hitachi 270–50 IR spectrophotometer.

Preparation of thiosemicarbazides (IIa–c)

A suspension of acid hydrazide (0.05 mole) in rectified spirit (25 mL) was treated with appropriate isothiocyanate (0.1 mole) and heated under reflux for 2 h. The thiosemicarbazide separated was collected and dried.

IR: 1200 cm^{-1} ν(C—S), 1680 cm^{-1} ν(C=O), 3300 cm^{-1} ν(N—H)

1,2-Bis-(4-alkyl/allyl/aryl-5-mercapto-1,2,4-triazole) ethanes (IIIa–c)

Thiosemicarbazides (IIa–c) (0.005 mole) was heated under gentle reflux with aqueous NaOH (4%, 33 mL) for 1 h. The clear solution after treatment with activated charcoal was filtered and cooled. The filtrate was acidified with acetic acid.

IR: 1580 cm^{-1} ν(C—N), 2650 cm^{-1} ν(S—H), 3290 cm^{-1} ν(N—H)

1,2-Bis-(4-amino-5-alkyl/allyl/arylamino-1,2,4-triazole) ethane (IVa–c)

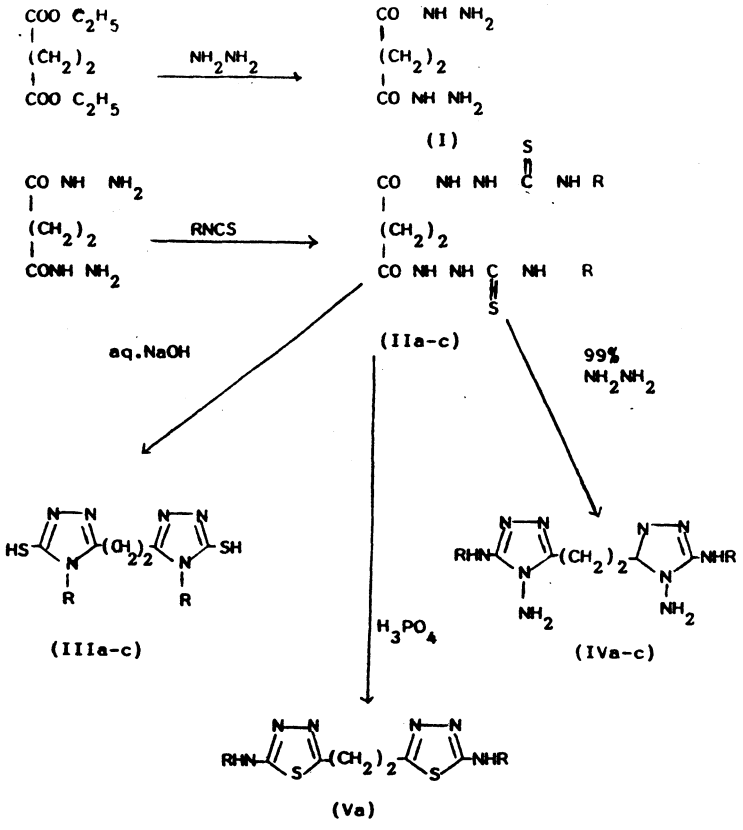
Thiosemicarbazide (IIa–c) (0.005 mole) was heated under gentle reflux with 99% hydrazine hydrate (10 mL) for 1 h. The resulting solution was cooled and poured to ice water, then acidified with acetic acid. The white solid separated out was filtered and dried.

IR: 1560 cm^{-1} ν(C=N), 3210 cm^{-1} ν(N—H)

1,2-Bis-(5-*p*-chlorophenyl amino-1,2,4-thiadiazole) ethanes (Va)

Thiosemicarbazide (IIa) (0.005 mole) was added gradually to anhydrous orthophosphoric acid (20 mL) in about 30 min. The reaction mixture was then heated at 120–130°C for 30 min in an oil bath. The resulting slurry was poured to ice cold water and stirred. The crude solid thus separated was collected (Va).

IR: 1040 cm^{-1} ν(C—S), 1590 cm^{-1} ν(C=N), 3300 cm^{-1} ν(N—H)



SCHEME I
R: (a) 4-chlorophenyl, (b) CH_3, (c) $CH{=}CH_2$.

TABLE-1
PHYSICAL DATA OF SYNTHESIZED COMPOUNDS

Comp. No.	R	m.p. (°C)	Molecular formulae
IIa	*p*-Chlorophenyl	178	$C_{18}H_{18}O_2N_6S_2Cl_2$
IIb	Methyl	>300	$C_8H_{16}O_2N_6S_2$
IIc	Allyl	176	$C_{10}H_{16}O_2N_6S_2$
IIIa	*p*-Chlorophenyl	236	$C_{18}H_{14}N_6S_2Cl_2$
IIIb	Methyl	>300	$C_8H_{12}N_6S_2$
IIIc	Allyl	271	$C_{10}H_{12}N_6S_2$
IVa	*p*-Chlorophenyl	215	$C_{18}H_{18}N_{10}Cl_2$
IVb	Methyl	>300	$C_8H_{16}N_{10}$
IVc	Allyl	275	$C_{10}H_{16}N_{10}$
Va	*p*-Chlorophenyl	236	$C_{18}H_{14}N_6S_2Cl_2$

Preparation of K-salt of oxalyl hydrazide (VI)

Mixture of oxalyl hydrazide (0.05 mole), CS_2 (0.075 mole) and KOH/ C_2H_5OH (0.075 mole/21 mL) were stirred together for 8 h at room tempereature. The salt obtained was filtered and dried (VI).

IR: 1070 cm^{-1} ν(C—S), 1620 cm^{-1} ν(C=O), 3300 cm^{-1} ν(N—H)

Bis-(4-amino substituted 5-mercapto-1,2,4-triazole) (VII a–b)

1 : 1 Potassium salt (VI) (0.002 mole) and substituted amines (0.002 mole) were refluxed for 20 min under low flame. The resulting suspension was poured to ice water and was acidified with acetic acid to get solid, which was filtered and dried (VIIa–b).

IR: 2650 cm^{-1} ν(S—H), 3290 cm^{-1} ν(N—H), 1560 cm^{-1} ν(C=N)

Preparation of methyl salt of oxalyl hydrazide (VIII)

Methyl iodide (0.01 mole) in methanol was added to (VI) (0.005 mole) and stirred for 1 h and was decomposed in ice water to get methyl salt (VIII).

IR: 1060 cm^{-1} ν(C—S), 1610 cm^{-1} ν(C=O), 3300 cm^{-1} ν(N—H)

Bis-(5-mercapto-1,3,4-oxadiazole) (IX)

Salt (VI) (0.005 mole) was refluxed with KOH (0.0375 mole) in ethanol for 18 h. The resultant was neutralised by treating with acetic acid and the solid obtained was filtered.

IR: 1620 cm^{-1} ν(C=N), 2650 cm^{-1} ν(S—H)

Bis-(5-substituted benzoic acid-1,3,4-oxadiazole) (Xa–b)

Oxalyl hydrazide (0.0015 mole) was refluxed with 2/4-substituted benzoic acid (0.03 mole) in presence of $POCl_3$ for 8 h. The resultant was product poured to ice and the pH 7 was maintained by adding liquid ammonia. The solid separated was collected.

Bis-(4-amino-substituted 5-substituted benzoic acid-1,2,4-triazole) (XIa–d)

1 : 2 Ratio of (Xa–b) (0.0025 mole) and substituted amines (0.005 mole) was refluxed for 20 min under low flame. Resultant was then poured to ice water and was acidified with acetic acid. Solid thus obtained was collected.

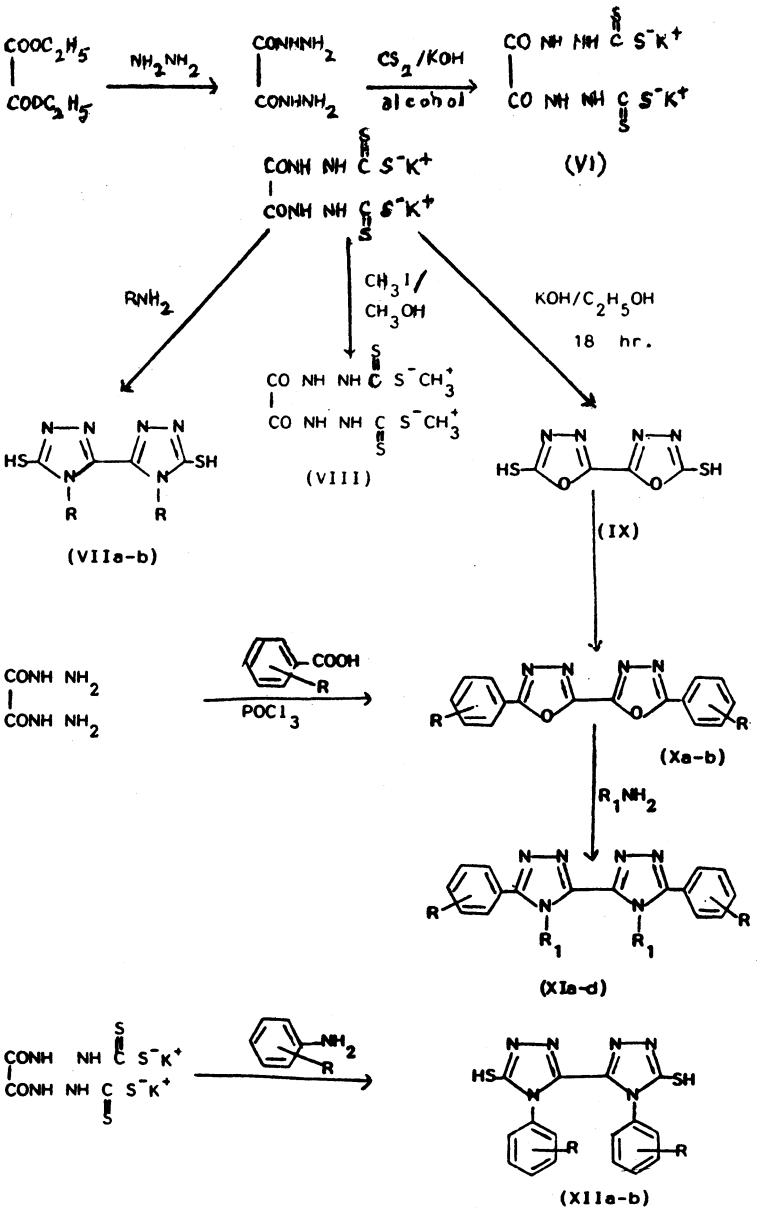
IR: 1620 cm^{-1} ν(C=N), 3400 cm^{-1} ν(N—H)

Bis-(4-substituted anilino-5-mercapto-1,2,4-triazole) (XIIa–b)

1 : 2 Potassium salt (VI) (0.0035 mole) and substituted aniline (0.007 mole) was refluxed for 3 h and was poured to crushed ice. The resultant was acidified with acetic acid. The solid separated was filtered.

IR: 1620 cm^{-1} ν(C=N), 2650 cm^{-1} ν(S—H), 3300 cm^{-1} ν(N—H)

In view of significant activity of bis-heterocycles we now report the anti-microbial and anthelmintic screening of the above bis-triazoles, bis-thiadiazoles and bis-oxadiazoles.



Scheme II

TABLE-2
PHYSICAL DATA OF SYNTHESISED COMPOUNDS

Comp No.	R	R_1	m.p. (°C)	Molecular formulae
VI	—	—	175	$C_4H_4N_4S_4K_2O_2$
VIIa	—NH_2	—	212	$C_4H_6N_8S_2$
VIIb	—C_6H_4NH	—	>300	$C_{16}H_{14}N_8S_2$
VIII	—	—	217	$C_6H_{10}N_4O_2S_4$
IX	—	—	175	$C_4H_2N_4O_2S_2$
Xa	-2-Chloro	—	143	$C_{16}H_8N_4O_2Cl_2$
Xb	-4-Chloro	—	191	$C_{16}H_8N_4O_2Cl_2$
XIa	-2-Chloro	—NH_2	96	$C_{16}H_{12}N_8Cl_2$
XIb	-2-Chloro	—NH·C_6H_5	151	$C_{28}H_{20}N_8Cl_2$
XIc	-4-Chloro	—NH_2	151	$C_{16}H_{12}N_8Cl_2$
XId	-4-Chloro	—NH·C_6H_5	193	$C_{28}H_{20}N_8Cl_2$
XIIa	-2-Chloro	—	>300	$C_{16}H_{12}N_8S_2Cl_2$
XIIb	-4-Chloro	—	95	$C_{16}H_{12}N_8S_2Cl_2$

Antimicrobial activity

Antibacterial activity is carried out against gram +ve organism, *e.g.*, *S. aureus* and gram –ve organisms *e.g.*, *Klebsiella*, *P. vulgaris* and *E. coli.*

Thiosemicarbazide of succinyl hydrazide with allyl isothiocyanate (IIc) and 1,2-bis-(4-amino-5-*p*-chlorophenylamino-1,2,4-triazole) ethanes (IVa) showed significant activity against *Klebsiella* and all other were less active.

Sample number IIa, IIc, VIIb, XIc and XId were highly active against *P. vulgaris* and all others showed moderate to weak activity.

Sample numbers VIII, IX, Xa, Xb, XIb, XIc and XId were highly active against *E. coli* and remaining were moderately active.

Sample numbers IIa, IIc, IIIb, IIIc, IVb, IVc, VI, VIIa, VIII, IX and XId were moderately active against *S. aureus.*

Most of the samples showed good activity against gram –ve organisms in comparison with that of gram +ve organisms.

The compounds having —NH_2, aromatic ring and halide substituent showed good activity because of the presence of halide substituent at *para* position on aromatic ring and also due to presence of amine group. The compunds bearing mercapto group showed insignificant activity.

Antifungal activity

Antifungal activity is carried out against *A. Niger* and none of the compounds showed significant activity.

Anthelmintic activity

Anthelmintic activity against *Pheretima posthuma* showed some interesting results.

Sample numbers IIc, IIIc, IIIa, IX and XIc were highly active, Xa, Xb were moderately active and remaining were inactive.

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