Bis Heterocycles as Potential Chemotherapeutic Agents. X. Synthesis of Bis(4-arylthiosemicarbazido)-, Bis(2-arylamino-1,3,4-thiadiazol-5-yl) and Bis(4-aryl-1,2,4-triazolin-3-thione-5-yl)pentanes and Related Compounds.

Vishnu J. Ram*

Medicinal Chemistry Division, Central Drug Research Institute, Lucknow 226001, India

Lallan Mishra, N. H. Pandey and D. S. Kushwaha

Department of Chemistry, S. C. Post-Graduate College, Ballia 227001, India

Luc A. C. Pieters and Arnold J. Vlietinck

Department of Pharmaceutical Sciences, Universiteitsplein 1, B-2610 Antwerpen, Belgium

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Synthesis of several bis(4-arylthiosemicarbazido- **1**, bis(2-arylamino-1,3,4-thiadiazol-5-yl)- **5** and bis(4-aryl-1,2,4-triazolin-3-thione-5-yl)- **2** pentanes is described. Sulphides **3** and sulphones **4** are also prepared from **2** by alkylation and subsequent oxidation with hydrogen peroxide respectively.

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Among azoles, triazoles and thiadiazoles are known to have antifungal [1,3], antibacterial [4,6] and insecticidal [7] properties. The antimicrobial properties of azoles mainly depend upon the nature of the functional group and their point of attachment. Dobosz [8] has recently reported the antitubercular activity of 1,2,4-triazoles in which the 4-position of the triazole ring is substituted either with a thiosemicarbazido function of bridged with a methylene group at the 5-position of another triazole ring.

Recently it has been reported [9] that sulphides and sulphones derived from 1,2,4-triazoline-5-thione possess remarkable pesticidal activity. Taking these structural features into consideration it was thought worthwhile to synthesize bis(4-aryl-1,2,4-triazoline-3-thione-5-yl)pentane **2**, their sulphides **3** and sulphones **4** as well as bis(2-arylamino-1,3,4-thiadiazol-5-yl)pentanes **5** to study their antimicrobial activities.

Compound **1** obtained [10,11] by the reaction of pimaloyl hydrazide with arylisothiocyanate was cyclized with alkali and *ortho*phosphoric acid to give bis(4-aryl-

Scheme – 1

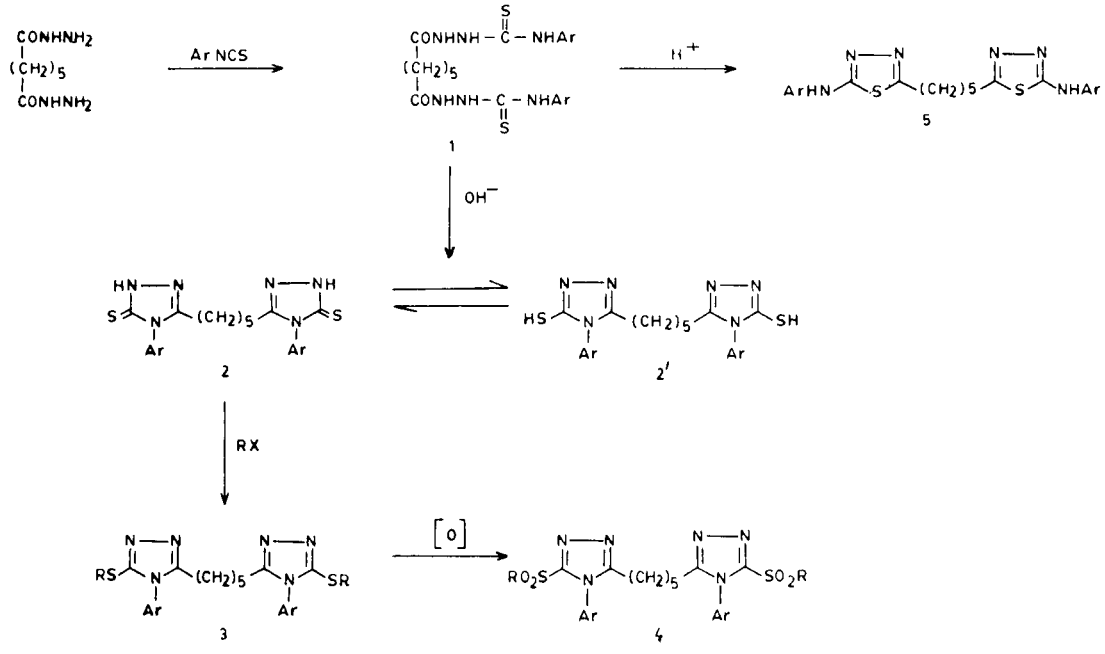

Table I

4, 4'-Diarylpimaloylthiosemicarbazides **1** and Bis(4-aryl-1,2,4-triazoline-3-thione-5-yl)pentane **2**

Compound No.	Ar	MP °C	Molecular Formula	M^+	Elemental analysis (%) Calcd. C	H	N	Found C	H	N
1b	*o*-Tolyl	135	$C_{23}H_{30}N_6O_2S_2$	486	56.17	6.21	17.27	56.33	6.29	17.44
1c	*m*-Toyl	174	$C_{23}H_{30}N_6O_2S_2$	486	56.17	6.21	17.27	56.42	6.14	17.32
1d	*m*-Fluorophenyl	177	$C_{21}H_{24}N_6F_2O_2S_2$	494	51.00	4.89	16.99	51.37	4.77	16.86
2b	*o*-Tolyl	307-308	$C_{23}H_{26}N_6S_2$	450	61.30	5.82	18.65	61.42	5.88	18.87
2d	*m*-Fluorophenyl	232	$C_{21}H_{20}N_6F_2S_2$	458	55.01	4.40	18.33	55.27	4.66	18.47

Table II

Bis(4-aryl-3-alkylthio-1,2,4-triazol-5-yl)pentane **3** and Bis (4-aryl-3-alkylsulphonyl-1,2,4-triazol-5-yl) pentane **4**

Compound No.	Ar	MP °C	Molecular Formula	M^+	Elemental analysis (%) Calcd. C	H	N	Found C	H	N
		Ar = Phenyl								
3d	Allyl	89-100	$C_{27}H_{30}N_6S_2$	502	64.51	6.02	16.72	64.74	6.11	16.49
3e	Benzyl	86-87	$C_{35}H_{34}N_6S_2$	602	69.74	5.69	13.94	69.98	5.71	13.77
3f	*p*-Chlorobenzyl	63	$C_{35}H_{32}Cl_2N_6S_2$	671	62.58	4.80	12.51	62.64	4.94	12.61
3g	*p*-Nitrobenzyl	96	$C_{35}H_{32}N_8O_4S_2$	692	60.68	4.66	16.17	60.49	4.39	16.02
3h	2-Nitro-4-tri-flouoromethylphenyl	164	$C_{35}H_{26}F_6N_8S_2O_4$	800	52.50	3.27	13.99	52.31	3.44	13.79
3i	2,4-Dinitrophenyl	221	$C_{33}H_{26}N_{10}S_2O_8$	754	52.52	3.47	18.56	52.62	3.49	18.71
		Ar = *o*-Toyl								
3j	Methyl	58	$C_{25}H_{30}N_6S_2$	478	62.73	6.32	17.59	62.75	6.34	17.59
		Ar = m-Toyl								
3k	Methyl	119-120	$C_{25}H_{30}N_6S_2$	478	62.73	6.32	17.56	62.71	6.31	17.59
3l	Ethyl	98-100	$C_{27}H_{34}N_6S_2$	506	64.00	6.76	16.58	64.39	6.84	16.44
3m	*n*-Butyl	74	$C_{31}H_{42}N_6S_2$	562	66.15	7.52	14.93	66.33	7.59	14.63
3n	Benzyl	83-84	$C_{37}H_{38}N_6S_2$	630	70.44	6.07	13.32	70.22	6.21	13.44
3o	*p*-Chlorobenzyl	110-111	$C_{37}H_{36}Cl_2N_6S_2$	699	63.51	5.19	12.01	63.71	5.31	12.08

Table II (continued)

Compound No.	Ar	MP °C	Molecular Formula	M+	Elemental analysis (%) Calcd. C	H	N	Found C	H	N
		Ar = Fluoro-phenyl								
3p	*n*-Butyl	113-114	$C_{29}H_{36}F_2N_6S_2$	570	61.03	6.36	14.72	61.40	6.57	14.55
3q	Benzyl	126-127	$C_{35}H_{32}F_2N_6S_2$	638	65.81	5.05	13.16	65.71	5.14	13.13
3r	*p*-Nitrobenzyl	120	$C_{35}H_{30}F_2N_8O_4S_2$	728	57.68	4.15	15.37	57.44	4.22	15.48
3s	2-Nitro-4-trifluoro-methylphenyl	164	$C_{35}H_{24}F_8N_8O_4S_2$	836	50.25	2.89	13.99	50.35	2.91	13.71
3t	*p*-Nitrophenyl	83-84	$C_{33}H_{26}F_2N_8O_4S_2$	700	56.56	3.74	15.99	56.44	3.78	15.74
3u	2,4-Dinitrophenyl	229	$C_{33}H_{24}F_2N_{10}O_8S_2$	790	50.13	3.06	17.71	50.39	3.14	17.89
		Ar = Phenyl								
4b	Ethyl	154	$C_{25}H_{30}N_6O_4S_2$	542	55.33	5.57	15.49	55.48	5.69	15.86
4c	*n*-Butyl	125-126	$C_{29}H_{38}N_6O_4S_2$	598	58.17	6.40	14.03	58.43	6.64	14.21
4d	Benzyl	169-170	$C_{35}H_{34}N_6O_4S_2$	666	63.04	5.14	12.60	63.14	5.19	12.64
4e	*p*-Nitrobenzyl	75	$C_{35}H_{32}N_8O_4S_2$	756	55.55	4.26	14.81	55.77	4.23	14.93
4f	*p*-Chlorobenzyl	110	$C_{35}H_{32}Cl_2N_6O_4S_2$	735	57.14	4.38	11.42	57.01	4.39	11.49
4g	2-Nitro-4-trifluo-romethylphenyl	239	$C_{35}H_{26}F_6N_8O_8S_2$	864	48.61	3.03	12.96	48.44	3.13	12.87
4h	2,4-Dinitrophenyl	241	$C_{33}H_{26}N_{10}O_{12}S_2$	818	48.41	3.20	17.11	48.66	3.39	17.44
		Ar = Fluoro-phenyl								
4i	*n*-Butyl	136	$C_{29}H_{36}F_2N_6O_4S_2$	634	54.87	5.72	13.24	54.49	5.61	13.29
4j	Benzyl	190	$C_{35}H_{32}F_2N_6O_4S_2$	702	59.82	4.59	11.96	59.67	4.33	11.84
4k	*p*-Nitrobenzyl	65	$C_{35}H_{30}F_2N_8O_8S_2$	792	53.03	3.81	14.13	53.14	3.77	14.22
4l	2-Nitro-4-trifluo-romethylphenyl	85	$C_{35}H_{24}F_8N_8O_8S_2$	900	46.67	2.69	12.44	46.41	2.77	12.39
4m	2,4-Dinitrophenyl	120	$C_{33}H_{24}F_2N_{10}O_{12}S_2$	854	46.37	2.83	16.39	46.71	2.81	16.44
		Ar = *m*-Tolyl								
4n	Benzyl	121-122	$C_{37}H_{38}N_6O_4S_2$	694	63.96	5.51	12.09	63.87	5.90	12.14
4o	*p*-Chlorobenzyl	173	$C_{37}H_{36}Cl_2N_6O_2S_2$	763	58.19	4.75	11.00	58.27	4.81	11.24

1,2,4-triazoline-3-thione-5-yl)pentane **2** and bis(2-aryl-amino-1,3,4-thiadiazol-5-yl)pentane **5** respectively. The thiones **2** were transformed into sulphides **3** by reaction with alkyl and aralkyl halides in alcoholic sodium hydroxide or DMF/anhydrous sodium carbonate. The resulting sulphides **3** were oxidized [11] to sulphones **4** with 3% acidic potassium permanganate or hydrogen peroxide. The latter oxidizing agent was found superior to acidic potassium permanganate in respect to purity and yield of the sulphones.

The ir spectra of bis-thiosemicarbazides **1** showed three characteristic peaks at 3250-3150, 2980-2900 and 1700-1650 cm^{-1} due to -NH, -OH and >C=O stretching frequency respectively. Complete disappearance of carbonyl frequency was noticed in **2** and **5** after the base and acid cyclizaton of **1**. Absence of peaks in the region 2600-2550 cm^{-1} in **2** excluded the possibility of the thiol form **2'** in the solid state.

All the compounds were screened for antifungal activity against *Candida albicans, Cryptococcus neoformans, Saporotrichum schenckii, Trichophyton mentagrophytes and Aspergillus fumigatus* at the concentration of 100 μg/ml and antibacterial activity against *Streptococcus faecalis, Klebsiella pneumoniae, Escherichia coli, Pseudomonas aeruginosa* and *Staphylococcus aureus* at 100 μg/ml but none of the compounds exhibited worth mentioning activity.

EXPERIMENTAL

Melting points were determined in an open capillary on a Thomas Hoover apparatus and are uncorrected. The ir spectra were recorded on a Perkin-Elmer spectrometer 137E. The ^{1}H-nmr spectra of the compounds were obtained from a Perkin-Elmer R-32 spectrometer using TMS as internal standard and the ^{13}C spectra of some compounds were recorded on a Brücker WM-400. Mass spectra were recorded on a Jeol JMSD-300 spectrometer.

4,4'-Diphenylpimaloylthiosemicarbazide (**1a**).

A solution of pimaloylhydrazide (1.88 g, 10 mmoles) in 20 ml of ethanol was refluxed with phenylisothiocyanate (2.8 g, 21 mmoles) for 2 hours. During this period, the precipitate was filtered after cooling. The crude product was washed with ethanol and finally crystallized from DMF:water, yield 3.6 g (79%), mp 173°; ms: m/z 458 (M^+) ^{13}C nmr (DMSO-d_6): δ 181.15 (s, C=O), 171.79 (s, C=S), 127.96 (s, C_3 and C_5 aryl), 139.08 (s, C_1-aryl), 124.8 (s, C_2, C_4 and C_6-aryl), 33.12 (s, C_1 and C_5-pentyl), 28.24 (s, C_2 and C_4-pentyl), 24.23 (s, C_3-pentyl).

Anal. Calcd. for $C_{21}H_{26}N_6O_2S_2$: C, 55.00; H, 5.71; N, 18.32. Found: C, 55.22; H, 5.81; N, 18.45.

Other compounds prepared in this series are listed in Table 1, **1b-d**, along with their relevant data.

Bis(4-phenyl-1,2,4-triazoline-3-thione-5-yl)pentane (**2a**).

A solution of 4,4'-diphenylpimaloylthiosemicarbazide (**1a**, 2.0 g) in 5*N* aqueous sodium hydroxide (25 ml) was refluxed for 3 hours and filtered. The filtrate on neutralization with dilute hydrochloric acid provided a white precipitate which was filtered, washed with water and crystallized from ethanol, yield 75%, mp 225°; ms: m/z 422 (M^+); ir (potassium bromide): 3050 (γ NH), 2900 (γ CH), 1330, 1290 and 1100 cm^{-1} (C=S); ^{13}C nmr (DMSO-d_6): δ 67.7 (s, C_3-triazol ring), 151.89 (s, C_5-triazole ring), 133.69 (s, C_1-aryl), 129.34 (s, C_3 and C_5-aryl), 128.09 (s, C_2, C_4 and C_6-aryl), 27.21 (s, C_1 and C_5-pentyl), 24.87 (s, C_2 and C_4-pentyl), 24.5 (s, C_3-pentyl).

Anal. Calcd. for $C_{21}H_{22}N_6S_2$: C, 59.69; H, 5.25; N, 19.89. Found: C, 59.63; H, 5.19; N, 19.91.

Bis(4-*m*-tolyl-1,2,4-triazoline-3-thione-5-yl)pentane (**2c**).

This compound was prepared from **1c** (2.0 g) as described in the preceding experiment, yield 70%, mp 278-280°; ms: m/z 450 (M^+); ^{1}H nmr (DMSO-d_6): δ 1.1-1.5 (m, 6H, $3CH_2$), 2.13-2.43 (m, 10H, $2CH_3$ and $2CH_2$), 6.96-7.4 (m, 8H, ArH).

Anal. Calcd. for $C_{23}H_{26}N_6S_2$: C, 61.33; H, 5.78; N, 18.67. Found: C, 60.92; H, 5.83; N, 18.45.

Two other compounds, **2b,d**, thus prepared are listed in Table 1.

Bis(2-phenylamino-1,3,4-thiadiazol-5-yl)pentane (**5a**).

A solution of 4,4'-diphenylpimaloylthiosemicarbazide (**1a**, 2.25 g) in *ortho*phosphoric acid (15 ml) was warmed to 120-135° for an hour under stirring. The reaction content after cooling was poured on crushed ice and the white precipitate thus obtained was filtered, washed with water and isolated as phosphoric acid salt, yield 60%, mp 233-235°; ir (potassium bromide): 3250 (γ NH), 2950 (γ CH), 1610, 1560 (γ C=C, δ NH), 2950, 1060 (γ P=O).

Anal. Calcd. for $C_{21}H_{22}N_6S_2 \cdot 2H_3PO_4 \cdot H_2O$ (636): C, 39.62; H, 4.72; N, 13.21. Found: C, 39.95; H, 4.54; N, 13.63.

Bis(2-*o*-tolylamino-1,3,4-thiadiazol-5-yl)pentane (**5b**).

The title compound was obtained in 50% yield from the acid cyclization of 4,4'-di(*o*)tolylpimaloylthiosemicarbazide (**1b**) following the preceding procedure, mp 256°; ir (potassium bromide): 3250 (γ NH), 2950 (γ CH), 1610, 1560 (γ C=C, δ NH), 1040 cm^{-1} (γ P=O).

Anal. Calcd. for $C_{23}H_{26}N_6S_2 \cdot 2H_3PO_4 \cdot H_2O$ (664): C, 41.56; H, 5.12; N, 12.65. Found: C, 41.56; H, 5.23; N, 12.33.

Bis(2-*m*-tolylamino-1,3,4-thiadiazol-5-yl)pentane (**5c**).

The compound was obtained in 55% yield from the cyclization of **1c** in *ortho*phosphoric acid as described above, mp 208-210°; ir (potassium bromide): 3450 (γ NH), 2970 (γ CH), 1610, 1560 (γ C=C, δ NH), 1060 cm^{-1} (γ P=O).

Anal. Calcd. for $C_{23}H_{26}N_6S_2 \cdot 2H_3PO_4 \cdot 2 \cdot 5H_2O$ (691): C, 39.94; H, 5.36; N, 12.16. Found: C, 39.70; H, 5.04; N, 11.82.

Bis(4-phenyl-3-methylthio-1,2,4-triazol-5-yl)pentane (**3a**).

A solution of **2a** (1.0 g) in alcoholic sodium hydroxide (10 ml, 8%) was refluxed with methyl iodide (0.8 g) for 3 hours, cooled, poured into ice cold water and left overnight. The precipitate thus obtained was filtered, washed with water and finally crystallized from ethanol-water, yield 60%, mp 165°; ms: m/z 450 (M^+); ^{13}C nmr (DMSO-d_6): δ 155.22 (s, C_3-triazole), 151.89 (s, C_5-triazole), 133.69 (s, C_1-aryl), 129.34 (s, C_3 and C_5-aryl), 128.09 (s, C_2, C_4 and C_6-aryl), 27.21 (s, C_1 and C_5-pentyl), 24.87 (s, C_2 and C_4-pentyl), 24.5 (s, C_3-pentyl), 14.1 (s, 2, SCH_3).

Anal. Calcd. for $C_{23}H_{26}N_6S_2$: C, 61.30; H, 5.82; N, 18.65. Found: C, 61.57; H, 5.77; N, 18.73.

Bis(4-phenyl-3-ethylthio-1,2,4-triazol-5-yl)pentane (**3b**).

The title compound was prepared from the reaction of **2a** (1.0 g) and ethyl iodide as described in the preceding experiment. It was isolated as usual and crystallized from water-ethanol, yield 50%, mp 142-143°; ms: m/z 478 (M^+); ^{1}H nmr (deuteriochloroform): δ 1.1-1.4 (m, 12H, $2CH_3$ + $3CH_2$), 2.63 (t, 4H, $2CH_2$), 3.1 (q, 4H, S-CH_2), 7.0-7.6 (m, 10H, ArH).

Anal. Calcd. for $C_{25}H_{30}N_6S_2$: C, 62.76; H, 6.28; N, 17.57. Found: C, 63.00; H, 6.52; N, 17.73.

Bis(4-phenyl-3-*n*-butylthio-1,2,4-triazol-5-yl)pentane (**3c**).

A solution of **2a** (2.11 g) and anhydrous sodium carbonate (1.06 g) in DMF (15 ml) was treated with *n*-butyl bromide (1.37 g) and stirred at room temperature for 4 hours. The reaction content was poured into ice cold water and left overnight in a refrigerator. The oily product separated was triturated with water and finally crystallized from DMF-water, yield 75%, mp 110°; ms: m/z 534 (M^+); ^1H nmr (DMSO-d_6): δ 0.83 (t, 6H, $2CH_3$), 1.16-1.60 (m, 14H, $7CH_2$), 2.43 (t, 4H, $2CH_2$), 2.9 (t, 4H, SCH_2), 7.2-7.6 (m, 10H, ArH).

Anal. Calcd. for $C_{29}H_{38}N_6S_2$: C, 65.17; H, 7.12; N, 15.73. Found: C, 65.52; H, 7.11; N, 15.41.

Other compounds, **3d-u**, were prepared similarly and are listed in Table 2 along with their relevant data.

Bis(4-phenyl-3-methylsulphonyl-1,2,4-triazol-5-yl)pentane (**4a**).

A solution of **3a** (1.15 g) in a minimum quantity of glacial acetic acid (8 ml) was oxidized by dropwise addition of aqueous potassium permanganate solution (3%) until the violet colour persisted. The mixture was filtered, washed several times with water and finally crystallized with dilute acetic acid, yield 56%, mp 110-112°; ms: m/z 514 (M^+); ir (potassium bromide): 2930, 2860 (γ CH), 1600, 1500 (γ C=C, δ CH), 1160 cm^{-1} (γ S=O).

Anal. Calcd. for $C_{23}H_{26}N_6S_2O_4$: C, 53.69; H, 5.05; N, 16.34. Found: C, 54.04; H, 5.30; N, 16.51.

Other compounds, **4b-o**, thus prepared are listed in Table 2 along with their relevant data.

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