Pharmaceutical Research, Vol. 4, No. 4, 1987

Report

Synthesis and Biological Activity of Isodithiobiurets, Dithiobiurets, and Dithiazoles

Surendra N. Pandeya,[1,2] Ashok Kumar,[1] Bhav N. Singh,[1] and Dina N. Mishra[1]

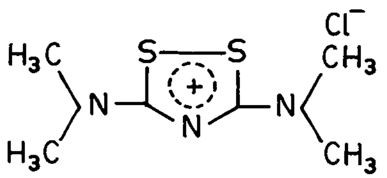
Received January 8, 1986; accepted March 16, 1987

A series of isodithiobiurets, dithiobiurets, and dithiazoles was synthesized and tested for biological activity. Generally, the compounds potentiated the hypnosis induced by pentobarbitone (50 mg/kg ip) in albino mice and exhibited antifungal and insecticidal activity against *Fusarium oxysporum* and *Periplanata americana*, respectively. Some compounds showed anticonvulsant and analgesic activity in albino rats.

KEY WORDS: isodithiobiurets; dithiobiurets; dithiazoles; pentobarbitone hypnosis effect; antifungal activity; insecticidal activity; anticonvulsant activity; analgesic activity.

INTRODUCTION

Acylureas and biurets are noncyclic compounds with anticonvulsant activity (1). Replacement of one or both oxygens with sulfur results in the formation of thiobiurets and dithiobiurets. This modification increases the lipophilicity and possibly the biological activity of these compounds. 1-Allyl-2-thiobiuret was shown to regulate the growth of germinating wheat and cucumber seeds (2). Further, Oliver and co-workers (3,4) reported the chemosterilizing action of some dithiobiuret and dithiazole derivatives in male house flies (*Musca domestica*). 3,5-Bis-(dimethylamino)-1,2,4-dithiazolium chloride (I) is considered to be a prototype for a new class of female antifertility agents (5). Other biological properties exhibited by dithiazoles and dithiazolidines are fungicidal, herbicidal, miticidal, and pesticidal activities (6).


(I)

Scheme I

The structural similarity of dithiobiuret to biurets led us to test several analogues for their potentiation of barbiturate hypnosis, antifungal activity against *Fusarium oxysporum*, and insecticidal activity against *Periplanata americana*. The intermediate isodithiobiurets have also been tested for these properties. Finally, as barbiturates are anticonvulsant agents (7), we tested these compounds for their anticonvulsive and analgesic activities as well.

None of the synthesized compounds has been previously described in the literature.

MATERIALS AND METHODS

All the melting points were determined in open capillaries and are uncorrected. IR spectra were recorded in Nujol using a Perkin–Elmer 621 spectrophotometer. UV spectra were obtained in ethanol using a Perkin–Elmer 402 spectrophotometer. 1,1-Dialkylthioureas were prepared as previously described (8). Benzylation of all the thioureas was accomplished by refluxing them with benzylchloride in ethanol (9). Isothiocyanates were prepared by standard methods (10).

1,1-Dialkyl-5-phenyl-2-*S*-benzyliso-4-thiobiuret (IIIa)

1,1-Dimethyl-2-*S*-benzylisothiourea (9.2 g, 0.04 mol) was suspended in benzene (100 ml) and the mixture was refluxed for 2 hr. Evaporation of the solvent yielded a semisolid mass which, after washing with petroleum ether and ethanol, afforded a crystalline solid. Crystals were obtained from ethanol. M.P., 134°C. Yield, 11.5 g (75%). *Anal.* Found: C, 61.78%; H, 5.45%; N, 12.68% for $C_{17}H_{19}N_3S_2$ requires C, 62%; H, 5.8%; N, 12.77%. IR (Nujol) V_{max}, cm^{-1}: 3200 (–NH), 1590 (C=N), 1520 (N–C=S), 1410 (C–S–O), 1240 (C=S). UV (EtOH) λ_{max}: 250 nm.

Other compounds (IIIb to IIIl) in the series were sythesized by the same procedure and are listed in Table I along with their physical constants.

Oxidation of 1,1-Dimethyl-5-phenyl-2-*S*-benzyliso-4-thiobiurets: Formation of 5-Dimethylamino-3-phenylimino-1,2,4-dithiazole Hydrobromide (IVa)

1,1-Dimethyl-5-phenyl-2-*S*-benzyliso-4-thiobiuret (IIIa)

---

[1] Department of Pharmaceutics, Institute of Technology, Banaras Hindu University, Varanasi 221 005, India.

[2] To whom correspondence should be addressed.

Table I. 1,1-Di-alkyl/aryl-5-aryl/alkyl-2-*S*-benzyliso-4-thiobiurets (III)

							Analysis, N (%)[a]	
Compound	R	R′	R″	M.P. (°C)	Yield (%)	Molecular formula	Required	Found
IIIa	$-CH_3$	$-CH_3$	$-C_6H_5$	134	75	$C_{17}H_{19}N_3S_2$	12.77	12.68
IIIb	$-CH_3$	$-CH_3$	$p-CH_3 \cdot C_6H_4$	140	70	$C_{18}H_{21}N_3S_2$	12.24	12.07
IIIc	$-CH_3$	$-CH_3$	$p-Cl \cdot C_6H_4$	170	72	$C_{17}H_{18}ClN_3S_2$	11.55	11.50
IIId	$-CH_3$	$-CH_3$	$-CH_3$	120	85	$C_{12}H_{17}N_3S_2$	15.73	15.56
IIIe	$-C_2H_5$	wC_2H_5	$-C_6H_5$	160	70	$C_{19}H_{23}N_3S_2$	11.76	11.68
IIIf	$-C_2H_5$	$-C_2H_5$	$p-CH_3 \cdot C_6H_4$	156	65	$C_{20}H_{25}N_3S_2$	11.32	11.08
IIIg	$-C_2H_5$	$-C_2H_5$	$-CH_2 \cdot C_6H_5$	101	60	$C_{20}H_{25}N_3S_2$	11.32	11.12
IIIh	H	$-C_6H_5$	$p-OC_2H_5 \cdot C_6H_4$	120	80	$C_{23}H_{23}N_3OS_2$	10.02	9.64
IIIi	H	$-C_6H_5$	$p-Br \cdot C_6H_4$	105	40	$C_{21}H_{18}BrN_3S_2$	9.23	8.85
IIIj[b]				153	32	$C_{23}H_{22}N_2S_2$	7.95	7.53
IIIk	H	$p-CH_3 \cdot C_6H_4$	$p-OC_2H_5 \cdot C_6H_4$	101	85	$C_{24}H_{25}N_3OS_2$	9.65	9.54
IIIl	H	$p-CH_3 \cdot C_6H_4$	$p-Br \cdot C_6H_4$	122	45	$C_{22}H_{20}BrN_3S_2$	8.93	8.48

[a] Satisfactory C and H analyses were also obtained for all the compounds.
[b] For structure see Scheme II.

(3.0 g) was made into a thin paste with chloroform (5 ml) and molecular bromine (2.5 g) was added portionwise with stirring. Debenzylation was evident from the evolution of lachrymatory fumes of benzylbromide. After half an hour, the reaction mixture was washed with chloroform and solvent ether to remove unreacted materials. The product was crystallised from ethanol. M.P., 254°C. Yield, 3.8 g (80%). *Anal.* Found: C, 37.55; H, 3.50; N, 13.13 for $C_{10}H_{12}N_3S_2Br$ requires C, 37.7; H, 3.7; N, 13.21. IR (Nujol) V_{max}, cm^{-1}: 1620 (C=N), 490 (ring S–S linkage). UV (EtOH) λ_{max}: 260 nm.

Using similar methods, other 1,2,4-dithiazoles (IVa to IVm) were prepared and are listed in Table II along with their physical constants.

Reduction of 1,1-Dimethyl-5-phenyl-2-*S*-benzyliso-4-thiobiuret (IIIa): Formation of 1,1-Dimethyl-5-phenyl-2,4-dithiobiuret (Va)

1,1-Dimethyl-5-phenyl-2-*S*-benzyliso-4-thiobiuret (10.0 g) was dissolved in a pyridine–triethylamine solution (70 ml, 6:1) and a stream of hydrogen sulfide gas was passed through it for 4 hr. The reaction mixture was poured over crushed ice and acidified with hydrochloric acid. The precipitated solid was filtered and crystallized from ethanol. M.P., 85°C. Yield, 4.0 g (55%). *Anal.* Found: C, 50.15; H, 5.38; N, 17.23 for $C_{10}H_{13}N_3S_2$ requires C, 50.20; H, 5.43; N, 17.57. IR (Nujol) V_{max}, cm^{-1}: 3400 (NH), 1520 (N–C=S), 1240 (C=S). UV (EtOH) λ_{max}: 280 nm.

A similar procedure was adopted for the synthesis of other compounds in this series (Va to Vp) and they are listed in Table III along with their physical constants.

Oxidation of 1,1-Dimethyl-5-phenyl-2,4-dithiobiuret (Va): Alternate Synthesis of 5-Dimethylamino-3-phenylimino-1,2,4-dithiazole Hydrobromide (IVa).

1,1-Dimethyl-5-phenyl-2,4-dithiobiuret (5.0 g) was dissolved in ethanol, and a solution of bromine (1 ml) in ethanol (10 ml) was added dropwise with constant stirring until the

Table II. 5-Di-alkyl/aryl-amino-3-aryl/alkyl-imino-1,2,4-dithiazole Hydrobromides (IV)

							Analysis, N (%)[a]	
Compound	R	R′	R″	M.P. (°C)	Yield (%)	Molecular formula	Required	Found
IVa	$-CH_3$	$-CH_3$	$-C_6H_5$	254	80	$C_{10}H_{12}BrN_3S_2$	13.20	12.92
IVb	$-CH_3$	$-CH_3$	$p-CH_3 \cdot C_6H_4$	244	75	$C_{11}H_{14}BrN_3S_2$	12.65	12.39
IVc	$-CH_3$	$-CH_3$	$p-Cl \cdot C_6H_4$	246	82	$C_{10}H_{11}BrN_3S_2Cl$	11.51	11.42
IVd	$-CH_3$	$-CH_3$	$-CH_3$	234	70	$C_5H_{10}BrN_3S_2$	16.40	16.18
IVe	$-C_2H_5$	$-C_2H_5$	$-C_6H_5$	230	81	$C_{12}H_{16}BrN_3S_2$	12.13	11.85
IVf	$-C_2H_5$	$-C_2H_5$	$p-CH_3 \cdot C_6H_4$	246	76	$C_{13}H_{18}BrN_3S_2$	11.66	11.23
IVg	$-C_2H_5$	$-C_2H_5$	$-CH_2 \cdot C_6H_5$	220	70	$C_{13}H_{18}BrN_3S_2$	11.66	11.3
IVh	H	$-C_6H_5$	$p-OC_2H_5C_6H_4$	175	70	$C_{16}H_{16}BrN_3OS_2$	10.24	10.35
IVi	H	$-C_6H_5$	$p-Br \cdot C_6H_4$	220	80	$C_{14}H_{11}Br_2N_3S_2$	9.43	9.14
IVj[b]				162	76	$C_{16}H_{14}N_2S_2$	9.30	9.20
IVk	H	$p-CH_3 \cdot C_6H_4$	$p-OC_2H_5 \cdot C_6H_4$	142	80	$C_{17}H_{18}BrN_3OS_2$	9.90	9.58
IVl	H	$p-CH_3 \cdot C_6H_4$	$p-Br \cdot C_6H_4$	157	75	$C_{15}H_{13}Br_2N_3S_2$	9.15	9.05
IVm[b]				188	83	$C_{15}H_{12}N_2S_2$	9.85	9.50

[a] Satisfactory C and H analyses were also obtained for all compounds.
[b] For structure see Scheme II.

Table III. 1,1-Di-alkyl/aryl-5-aryl/alkyl-2,4-dithiobiurets (V)

Compound	R	R′	R″	M.P. (°C)	Yield (%)	Molecular formula	Analysis, N (%)[a]	
							Required	Found
Va	$-CH_3$	$-CH_3$	$-C_6H_5$	85	50	$C_{10}H_{13}N_3S_2$	17.57	17.48
Vb	$-CH_3$	$-CH_3$	$p-CH_3 \cdot C_6H_4$	102	48	$C_{11}H_{15}N_3S_2$	16.60	16.32
Vc	$-CH_3$	$-CH_3$	$p-Cl \cdot C_6H_4$	104	55	$C_{10}H_{12}Cl \cdot N_3S_2$	15.35	15.13
Vd	$-CH_3$	$-CH_3$	$-CH_3$	125	50	$C_5H_{11}N_3S_2$	23.72	23.57
Ve	$-C_2H_5$	$-C_2H_5$	$-C_6H_5$	135	55	$C_{12}H_{17}N_3S_2$	15.73	15.45
Vf	$-C_2H_5$	$-C_2H_5$	$p-CH_3 \cdot C_6H_4$	110	54	$C_{13}H_{19}N_3S_2$	14.94	14.73
Vg	$-C_2H_5$	$-C_2H_5$	$-CH_2 \cdot C_6H_5$	122	55	$C_{13}H_{19}N_3S_2$	14.94	14.68
Vh	H	$-C_6H_5$	$p-C_2H_5O \cdot C_6H_4$	125	65	$C_{16}H_{17}N_3OS_2$	12.68	12.15
Vi	H	$-C_6H_5$	$p-Br \cdot C_6H_4$	140	60	$C_{14}H_{12}BrN_3S_2$	11.47	11.15
Vj[b]				132	56	$C_{16}H_{15}N_2S_2$	9.36	9.18
Vk	H	$p-CH_3 \cdot C_6H_4$	$p-OC_2H_5 \cdot C_6H_4$	142	58	$C_{17}H_{19}N_3OS_2$	12.17	12.05
Vl	H	$p-CH_3 \cdot C_6H_4$	$p-Br \cdot C_6H_4$	165	55	$C_{15}H_{14}BrN_3S_2$	11.05	10.87
Vm	H	$-C_6H_{11}$[c]	$-C_6H_5$	150	65	$C_{14}H_{19}N_3S_2$	14.33	14.15
Vn	H	$-C_6H_{11}$[c]	$p-OC_2H_5C_6H_4$	163	60	$C_{16}H_{23}N_3OS_2$	12.46	12.40
Vo	H	$-C_6H_{11}$[c]	$p-Br \cdot C_6H_4$	155	55	$C_{14}H_{18}BrN_3S_2$	11.29	11.12
Vp	H	$p-SO_2NH_2 \cdot C_6H_4$	$m-CH_3 \cdot C_6H_4$	140	75	$C_{15}H_{16}N_4O_2S_3$	11.05	11.01

[a] Satisfactory C and H analyses were also obtained for all the compounds.

[b] For structure see Scheme II.

[c] Cyclohexyl.

Table IV. Barbiturate Hypnosis Potentiation and Antifungal and Insecticidal Activities of Isodithiobiurets, Dithiobiurets, and 1,2,4-Dithiazoles

Compound[a]	Barbiturate hypnosis[b]			Antifungal activity (MIC, μg/ml)[c]	Insecticidal activity (mean KD time, hr)[d]
	Sleeping time (min; mean ± SE)		Potentiation (%)		
	Control	Treated			
IIIa	58.5 ± 4.8	131.5 ± 6.1	124.7*	50	8.1
IIIb	56.2 ± 3.2	102.3 ± 4.2	82.0*	10	10.2
IIIc	58.7 ± 5.1	121.2 ± 5.8	106.4*	25	9.5
IIId	60.8 ± 4.8	110.3 ± 5.2	81.4*	30	8.6
IIIe	63.2 ± 4.7	121.4 ± 4.6	92.0*	25	10.5
IIIf	63.2 ± 5.2	156.2 ± 5.8	147.1*	20	9.7
IIIg	61.4 ± 5.8	136.0 ± 4.8	121.4*	20	9.3
IIIh	54.0 ± 4.8	98.2 ± 5.3	81.8*	20	8.0
IIIi	58.1 ± 5.5	108.7 ± 4.6	87.0*	25	7.7
IIIj	63.2 ± 4.9	126.6 ± 5.1	100.3*	25	7.1
IIIk	56.0 ± 4.5	104.2 ± 3.9	86.0*	20	7.9
IIIl	57.0 ± 5.2	98.9 ± 4.2	73.5*	20	7.9
IVa	64.6 ± 3.3	90.2 ± 5.6	39.6**	25	8.8
IVc	64.1 ± 4.8	91.7 ± 6.2	43.0**	25	7.8
IVe	71.0 ± 4.6	149.6 ± 5.1	110.7*	20	10.2
IVg	66.2 ± 5.7	138.0 ± 4.6	108.4*	20	11.3
IVm	58.4 ± 5.6	71.3 ± 3.8	22.0[e]	100	10.7
Va	61.4 ± 5.2	146.2 ± 3.6	138.1*	15	10.8
Vb	61.2 ± 4.7	126.7 ± 4.2	107.0*	25	8.8
Vc	69.3 ± 4.6	143.0 ± 4.2	106.3*	50	9.7
Vf	59.2 ± 5.8	140.5 ± 4.8	137.3*	50	11.5
Vh	66.4 ± 4.8	161.2 ± 5.1	142.7*	20	6.5
Vi	63.4 ± 4.1	98.4 ± 4.8	55.2*	100	7.3
Vl	64.0 ± 4.5	96.1 ± 3.8	50.0*	20	7.4

[a] As in Tables I–III.

[b] Dose, 35 mg/kg ip ($N = 10$); pentobarbitone sodium (50 mg/kg ip)-induced hypnosis ($N = 10$).

[c] Percentage solution in acetone–water against *Fusarium oxysporum;* tolnaftate (MIC, 10 μg/ml).

[d] Dose, 0.5% acetone solution, ethyl parathion, mean KD time = 4.5 hr.

[e] Statistically insignificant.

* $P < 0.001$.

** $P < 0.01$.

reaction mixture turned yellowish brown in color. A solid separated and was crystallized from ethanol, M.P. 254°C. It did not lower the melting point when mixed with the sample obtained above.

Biological Activity

Potentiation of Barbiturate Hypnosis

Test compounds were suspended in propylene glycol and administered at doses of 35 mg/kg to male and female albino mice (20–30 g) which had been treated with pentobarbital sodium (50 mg/Kg, ip) to induce hypnosis. The drug effects were noticed 1 hr after their administration. The hypnosis was assessed as the time period between the loss and the regaining of the righting reflex. The increase in the sleeping time over that of the vehicle-administered pentobarbital group was taken as the index of potentiation. Student's *t* test was used to determine statistical significance (11).

Antifungal Activity

This activity was evaluated using the fungus *Fusarium oxysporum* employing Czapek Dox liquid growth medium mixed with test compounds. The growth was noticed after 12 hr by the hanging-drop method (12) for spore germination. The minimum inhibitory concentrations (MIC) were determined by serial dilution and the results are described in Table IV.

Insecticidal Activity

This test was performed (13) using adult male and female cockroaches (*Periplanata americana*). The test compounds were dissolved in acetone, and 0.02 ml of a 0.5% solution was administered (Table IV).

Anticonvulsant Activity

The screening method was as described by Swinyard and co-workers (14). Albino rats (100 to 150 g) of either sex were fasted 18 hr before each experiment. Supramaximal electroshock (150 mA, 0.2-sec duration) was given through a pair of corneal electrodes using a Techno Convulsiometer. The hind-limb extensor response was taken as the end point. Rats were prescreened 24 hr earlier and only those showing a positive extensor response were used. Test compounds, suspended in propylene glycol, were administered intraperitoneally, and the rats were subjected to electroshock after 1 hr.

Absence of the hind-limb extensor response was taken as an index of anticonvulsant activity. Significance of the results was evaluated using a chi-square test (11).

Analgesic Activity

Analgesic activity was determined in albino rats (100–150 g) of both sexes by the rat-tail hot-wire method (15) using a cutoff time of 30 sec. The test compounds were suspended in propylene glycol and administered in doses of 20 mg/kg, intraperitoneally. The latent period of the tail-flick

Table V. Anticonvulsant and Analgesic Activities of Isodithiobiurets, Dithiobiurets, and 1,2,4-Dithiazoles

	Anticonvulsant activity[b]		Analgesic activity[c]		
			Latent period of tail-flick response (sec; mean ± SE)		
Compound[a]	Protection (%)	*P* value	Control	Treated	*P* value
IIIa	50	NS[d]	6.93 ± 0.53	8.46 ± 0.80	NS
IIIc	0	—	9.56 ± 0.83	12.73 ± 0.56	0.025
IIIe	0	—	8.43 ± 0.43	10.63 ± 1.44	NS
IIIg	83	0.025	4.7 ± 0.04	7.46 ± 0.23	0.001
IIIh	100	0.01	7.23 ± 0.32	12.1 ± 1.32	0.01
IIIj	33	NS	8.6 ± 0.43	13.5 ± 1.48	0.01
IVa	33	NS	8.53 ± 0.29	12.03 ± 1.25	0.05
IVc	33	NS	10.76 ± 0.83	12.86 ± 1.27	NS
IVe	0	—	7.13 ± 0.78	12.17 ± 1.22	0.01
IVg	33	NS	11.2 ± 0.32	12.3 ± 1.10	NS
IVm	33	NS	11.3 ± 0.05	13.97 ± 0.44	0.001
Va	0	—	8.56 ± 0.29	10.60 ± 1.03	NS
Vb	0	—	8.80 ± 0.53	9.90 ± 0.26	NS
Vf	66	NS	8.16 ± 0.44	9.86 ± 0.20	0.01
Vg	0	—	8.73 ± 0.74	10.03 ± 0.43	NS
Vm	0	—	9.33 ± 0.51	13.16 ± 0.42	0.001
Vn	0	—	9.20 ± 0.56	9.93 ± 0.44	NS
Vo	33	NS	10.56 ± 0.86	15.83 ± 2.94	NS
Vp	33	NS	9.03 ± 0.77	14.43 ± 2.86	NS

[a] As in Tables I–III.

[b] Dose, 20 mg/kg ip for each compound ($N = 6$); phenobarbitone (30 mg/kg ip; 100% protection; $P < 0.01$, $N = 6$); phenetoin (60 mg/kg ip; 100% protection; $P < 0.01$, $N = 6$).

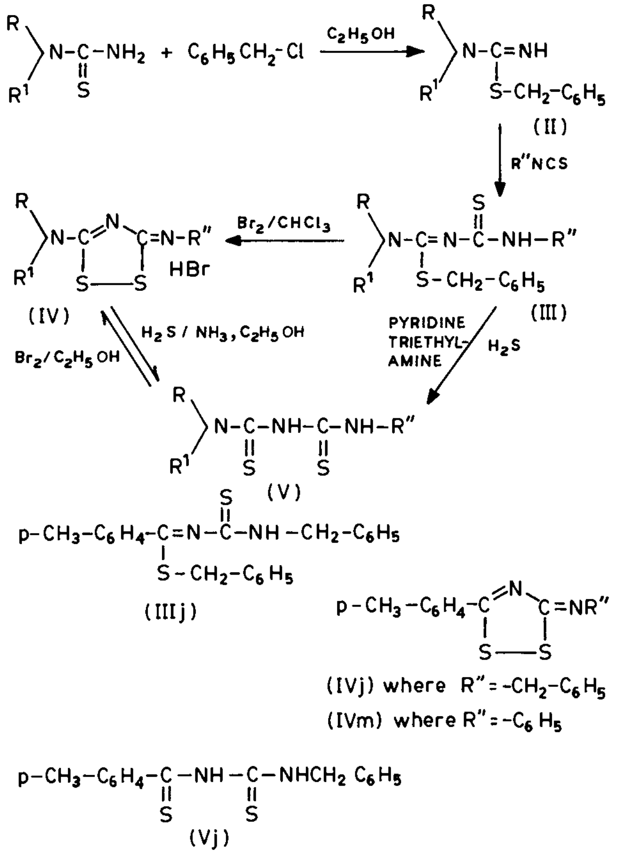
[c] Dose, 20 mg/kg ip for each compound ($N = 6$).

[d] Nonsignificant.

response was determined before and at 15, 30, 45, and 60 min after the administration of test compounds or the vehicle. The increase in latency of the tail-flick response was taken as an index of analgesic activity. The peak analgesic response was usually attained by 30 min, and this time point was used for data presentation and statistical analysis by the paired *t* test (11) (Table V).

RESULTS AND DISCUSSION

The compounds were synthesized by the following sequence of reactions.



Scheme II

1,1-Dialkylthioureas, when treated with benzylchloride in ethanol, gave 1,1-dialkyl-2-*S*-benzylisothioureas (II), which on treatment with aryl (or alkyl) isothiocyanates, furnished 1,1-dialkyl-5-aryl (or alkyl)-2-*S*-benzyliso-4-thiobiurets (III). These isodithiobiurets (III), upon oxidation with molecular bromine, afforded 5-dialkyl-amino-3-aryl (or alkyl)-imino-1,2,4-dithiazole hydrobromides (IV). The structures of these compounds were determined by alternative routes of synthesis, elemental analysis, and IR and UV spectra. The 1,2,4-dithiazoles, upon reduction with hydrogen sulfide gas in an ethanolic-ammonia solution, gave 1,1-dialkyl-5-aryl (or alkyl)-2,4-dithiobiurets (V). These dithiobiurets (V) were also directly synthesized by reduction of isodithiobiurets (III) with hydrogen sulfide gas in a pyridine–triethylamine solution. The dithiobiurets (V) were then converted into the corresponding 5-dialkylamino-3-aryl (or alkyl)-imino-1,2,4-dithiazole hydrobromides by oxidation with bromine in ethanol.

The relevant biological data of the test compounds are presented in Tables IV and V. Dithiobiurets were found to be generally more active than either isodithiobiurets or dithiazoles in the biological assays employed.

All the test compounds showed a prolongation of the pentobarbitone-induced sleeping time in albino mice (Table IV). The dithiazoles are less active in potentiating pentobarbitone-induced hypnosis. The dithiobiurets (except Vl and Ve) increase the sleeping time more than 100%, whereas with dithiazoles this increase is only 22 to 43% (except for VIg and IVe). Generally, the introduction of an electron-donating substituent in the para position of aromatic moieties increases activity. 1,1-Diethyl-5-*p*-tolyl-2-*S*-benzyliso-4-thiobiobiuret (IIIf) and 1-*p*-phenetyl-5-phenyl-2,4-dithiobiuret (Vh) were the most potent compounds in the respective series.

In tests of antifungal and insecticidal activities, the compounds gave promising results (Table IV). Many inhibited the growth of *Fusarium oxysporum* at between 20 and 30 μg/ml, and the most potent compound, 1,1-dimethyl-5-*p*-tolyl-2-*S*-benzyliso-4-thiobiuret (IIIb), was active at 10 μg/ml. This activity is equivalent to that of tolnaftate, the standard antifungal agent. Only two compounds, IVm and Vi, had rather high inhibitory concentrations (100 μg/ml) in the series. The compounds killed the test insect at between 6 and 11 hr; however, they were less potent than the standard insecticidal agent, ethyl parathion.

Anticonvulsant and analgesic data are presented in Table V. Compound IIIh was the most potent anticonvulsant agent (protection, 100%; $P < 0.010$, while compounds IIIc, IIIe, IVe, Va, Vb, Vg, Vm, and Vn had no measurable activity in this test. Compounds IIIa, IIIg, IIIj, IVa, IVc, IVg, IVm, Vf, Vo, and Vp were weakly active. Analgesic activity was detectable for compounds IIIc, IIIg, IIIh, IIIj, IVa, IVc, IVm, IVf, and Vm.

No structure–activity relationship could be readily discerned between any series of structures and their biological activities as measured.

ACKNOWLEDGMENTS

The authors are grateful to the University Grants Commission and the Council of Scientific and Industrial Research, New Delhi, for providing financial assistance to Dina N. Mishra and Ashok Kumar, respectively.

REFERENCES

1. W. J. Close and M. A. Spielman. In W. H. Hartung (ed.), *Medicinal Chemistry*, John Wiley and Sons, New York, 1961, Vol. 5, pp. 1–349.
2. E. Karanov and G. N. Vosilev. *Chem. Abstr.* 73:119454Y (1970).
3. J. E. Oliver, S. C. Chang, R. T. Braun, J. B. Strokes, and A. B. Borkovic. *J. Med. Chem.* 14:772–776 (1971).
4. J. E. Oliver, R. T. Braun, R. L. Fye, and A. B. Borkovic. *J. Agr. Food Chem.* 21:753–759 (1973).

5. D. W. Hahn, R. F. McConell, and J. L. McGuire. *Contraception* 21:529–537 (1980).
6. H. Bohme, H. Ahrensk, and H. H. Hotzel. *Arch. Pharm.* 307:748–755 (1974).
7. E. I. Isaacson and J. N. Delgado. In A. Burger (ed.), *Medicinal Chemistry*, 3rd ed., Pt. II, Wiley-Interscience, 1970, pp. 1386–1398.
8. P. W. Preisler. *J. Am. Chem. Soc.* 71:2849–2852 (1949).
9. E. W. Werner. *J. Chem. Soc.* 57:295–305 (1890).
10. A. I. Vogel. *A Text Book of Practical Organic Chemistry*, 3rd ed., ELBS and Longman Group, 1973, pp. 645–644.
11. P. K. Das and S. K. Bhattacharya. *J. Res. Ind. Med.* 9:83–98 (1974).
12. H. T. Hamilton. *Phytopathology* 21:445–451 (1931).
13. A. K. Ramrakhiani. *Ind. J. Pharm. Sci.* 49:16–17 (1978).
14. E. A. Swinyard, W. C. Brown, and L. S. Goodman. *J. Pharmacol. Exp. Ther.* 106:319–330 (1952).
15. O. L. Davies, J. Raventos, and A. L. Walpole. *Br. J. Pharmacol. Chemother.* 1:255–264 (1946).