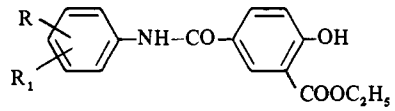
Table I.



No.	R	R_1	Mp, °C	Recrystallization solvent[a]	Formula	Analgetic activity (mice)[b,c]	Probability[d] $P \leq$
1	H	H	159-160	B	$C_{16}H_{15}NO_4$	37.1	<0.001
2	2Cl	H	154-155	A	$C_{16}H_{14}ClNO_4$	52.5	<0.001
3	3Cl	H	143-144	A	$C_{16}H_{14}ClNO_4$	56.4	≤0.001
4	4Cl	H	195-196	A	$C_{16}H_{14}ClNO_4$	32	<0.005
5	2Cl	3Cl	157-158	C	$C_{16}H_{13}Cl_2NO_4$	64.1	<0.001
6	2Cl	4Cl	164-165	C	$C_{16}H_{13}Cl_2NO_4$	74.3	<0.001
7	2Cl	5Cl	203-204	C	$C_{16}H_{13}Cl_2NO_4$	70.5	<0.001
8	2Cl	6Cl	200-201	C	$C_{16}H_{13}Cl_2NO_4$	62.8	<0.01
9	3Cl	4Cl	194-195	C	$C_{16}H_{13}Cl_2NO_4$	61.5	<0.01
10	3Cl	5Cl	185-186	C	$C_{16}H_{13}Cl_2NO_4$	67.9	<0.001
11	$2CH_3$	H	149-150	B	$C_{17}H_{17}NO_4$	55.1	<0.001
12	$3CH_3$	H	125-126	B	$C_{17}H_{17}NO_4$	51.2	<0.001
13	$4CH_3$	H	170-171	B	$C_{17}H_{17}NO_4$	37.1	<0.05
14	$2CH_3$	$3CH_3$	167-168	C	$C_{18}H_{19}NO_4$	46.1	≤0.01
15	$4OCH_3$	H	163-164	C	$C_{17}H_{17}NO_5$	44.8	<0.001
16	$4OC_2H_5$	H	165-166	C	$C_{18}H_{19}NO_5$	47.4	<0.001
17	$2CF_3$	H	160-161	B	$C_{17}H_{14}F_3NO_4$	42.3	≤0.001
18	$2CH_3$	5Cl	181-182	B	$C_{17}H_{16}ClNO_4$	46.1	<0.05
19	$2CH_3$	4Cl	178-179	B	$C_{17}H_{16}ClNO_4$	41	<0.001
20	$2CH_3$	3Cl	188-189	B	$C_{17}H_{16}ClNO_4$	41	<0.01
4HHA						48.7	<0.001

[a] A, MeOH; B, *i*-PrOH; C, AcOH. [b] Increase of reaction time % 3 hr after treatment. [c] Doses were of 30 mg/kg for each group of 10 mice. [d] The hot plate test counts were analyzed statistically by means of the Student *t* test. *P* was compared to controls.

0.05 mole of substituted anilines. The reaction mixture was refluxed for 2 hr and then diluted with cold H_2O, and the crystalline reaction product was filtered off. It was washed with 5% $NaHCO_3$ and recrystallized.

References

(1) G. B. Chesher, H. O. J. Collier, F. A. Robison, Taylor, S. E. Hunt, J. I. Jones, and A. S. Lindsey, *Nature (London)*, 175, 206 (1955).

(2) P. A. I. Janssen and A. Jageneau, *J. Pharm. Pharmacol.*, 9, 381 (1957).

(3) J. M. Z. Gladych and E. P. Taylor, *J. Chem. Soc.*, 4678 (1956).

Substituted Thiazolidones as Anticonvulsants†

C. Dwivedi,‡ T. K. Gupta, and Surendra S. Parmar*

Department of Pharmacology and Therapeutics, King George's Medical College, Lucknow University, Lucknow-3, India.

Received November 17, 1971

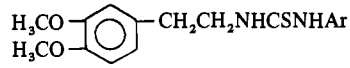
In continuation of our interest[1,2] in thiazolidones, some new 2-arylimino-3-(3,4-dimethoxyphenethyl)thiazolid-4-ones have been synthesized and tested for their anticonvulsant activity against pentylenetetrazol-induced seizures in albino mice.

Anticonvulsant activity was detd[2] by injecting the thiazolidone ip in a 5% aqueous suspension of gum acacia in groups of 10 mice of either sex. Pentylenetetrazol (80 mg/kg) was injected 4 hr after the administration of thiazolidones and the mice were then observed for 60 min for the occurrence of seizures. Animals devoid of even a threshold convulsion were considered protected. Anticonvulsant activity shown by substituted thiazolidones at 100 mg/kg is given in Table II. Compd 2 having an *o*-tolyl group at position 2 afforded the maximum protection of 70%, while administration in doses above or below 100 mg/kg caused lesser anticonvulsant activity. The low toxicity of this compound was reflected by its approximate LD_{50} (>2000 mg/kg).

†This investigation was supported in part with the financial assistance obtained from the Indian Council of Medical Research, New Delhi.

‡Junior Research Fellow of I.C.M.R., New Delhi.

Table I. Substituted Thiocarbamides



No.	Ar	Mp,[a] °C	Yield, %	Molecular formula[b]
1	C_6H_5	125	85	$C_{17}H_{20}N_2O_2S$
2	o-$CH_3C_6H_4$	112	65	$C_{18}H_{22}N_2O_2S$
3	m-$CH_3C_6H_4$	122	78	$C_{18}H_{22}N_2O_2S$
4	p-$CH_3C_6H_4$	92	85	$C_{18}H_{22}N_2O_2S$
5	3,4-$(CH_3)_2C_6H_3$	125	82	$C_{19}H_{24}N_2O_2S$
6	o-$OCH_3C_6H_4$	108	62	$C_{18}H_{22}N_2O_3S$
7	p-$OCH_3C_6H_4$	120	72	$C_{18}H_{22}N_2O_3S$
8	p-ClC_6H_4	114	80	$C_{17}H_{19}ClN_2O_2S$
9	p-BrC_6H_4	135	80	$C_{17}H_{19}BrN_2O_2S$
10	α-$C_{10}H_7$	166	68	$C_{21}H_{22}N_2O_2S$

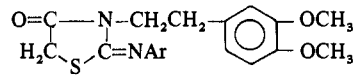
[a] Melting points were taken in open capillary tubes. [b] All compds were analyzed for C, H, and N and analyses were found within 0.4% of theory.

Experimental Section

1-Aryl-3-(3,4-dimethoxyphenethyl)thiocarbamide. 3,4-Dimethoxyphenethylamine (0.01 mole) was mixed with a suitable aryl isothiocyanate (0.01 mole) in 15 ml of dry PhH and was refluxed on a steam bath for 2 hr. The reaction mixt was concd under reduced pressure. The solid mass which sepd on cooling was filtered, washed (Et_2O, dil HCl), dried, and recrystd from EtOH. All thiocarbamides were characterized by their sharp melting points and elemental analyses (Table I).

2-Arylimino-3-(3,4-dimethoxyphenethyl)thiazolid-4-ones. A mixt of 1-aryl-3-(3,4-dimethoxyphenethyl)thiocarbamide (0.01 mole), $ClCH_2COOH$ (0.01 mole), and anhyd NaOAc (0.015 mole) in 15 ml of glacial AcOH was refluxed for 5–6 hr. The reaction mixt was poured into H_2O and refrigerated overnight. The sepd crude product was filtered, washed several times (H_2O), and recrystd from EtOH (Table II).

Table II. Substituted 4-Thiazolidones and Their Anticonvulsant Activity



No.	Ar	Mp,[a] °C	Yield, %	Molecular formula[b]	Protection, %	Mortality after 24 hr, %
1	C_6H_5	117	62	$C_{19}H_{20}N_2O_3S$	30	60
2	o-$CH_3C_6H_4$	126	55	$C_{20}H_{22}N_2O_3S$	70	20
3	m-$CH_3C_6H_4$	118	60	$C_{20}H_{22}N_2O_3S$	30	40
4	p-$CH_3C_6H_4$	160	64	$C_{20}H_{22}N_2O_3S$	40	50
5	3,4-$(CH_3)_2C_6H_3$	175	62	$C_{21}H_{24}N_2O_3S$	10	70
6	o-$OCH_3C_6H_4$	90	54	$C_{20}H_{22}N_2O_4S$	50	30
7	p-$OCH_3C_6H_4$	147	62	$C_{20}H_{22}N_2O_4S$	10	60
8	p-ClC_6H_4	150	60	$C_{19}H_{19}ClN_2O_3S$	60	50
9	p-BrC_6H_4	153	62	$C_{19}H_{19}BrN_2O_3S$	30	60
10	α-$C_{10}H_7$	128	58	$C_{23}H_{22}N_2O_3S$	50	40

[a,b] See footnotes to Table I.

Acknowledgments. The authors wish to express their thanks to Professor K. P. Bhargava and Dr. J. P. Barthwal for their advice and encouragement and to Dr. M. L. Dhar and Dr. Nitya Anand of the Central Drug Research Institute, Lucknow, for providing microanalysis facilities. Grateful acknowledgment is made to Dr. Edwin E. Hays, Gruppo Lepetit, Northridge, Calif., for a generous gift of research chemicals.

References

(1) R. Kumar, T. K. Gupta, and S. S. Parmar, *J. Pract. Chem.*, **312**, 201 (1970).
(2) S. S. Parmar, C. Dwivedi, A. Chaudhari, and T. K. Gupta, *J. Med. Chem.*, **15**, 99 (1972).

Synthesis of N′-Substituted Arylsulfonylpyrazoles, Their Anthelmintic Activity, and the Cytotoxicity of Some Hydrazides†

H. G. Garg* and Narendrajit Kaur

Department of Chemistry, University of Roorkee, Roorkee, India.
Received September 10, 1971

Our continued interest in the synthesis of biological active heterocycles has led us to study the synthesis and anthelmintic activity of N′-substituted arylsulfonyl-3,5-dimethyl-4-arylazopyrazoles. These compounds displayed anthelmintic and cytotoxicity activities of different magnitudes. All are apparently nontoxic to mice at the dosages used.

Experimental Section

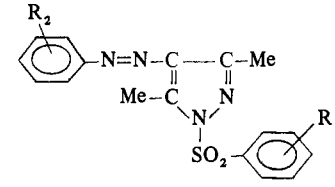
Melting points, taken with a Kofler hot-stage apparatus, are uncorr. Where analyses are indicated only by symbols of the elements, analytical result obtd for those elements were within ±0.4% of the calcd values.

2,3,4-Pentanetrione-3-arylhydrazons,[1] cinnamic acids, and hydrazides,[2] 3-nitro-4-methoxybenzenesulfonylhydrazide,[3] 3-chloro-4-methoxybenzenesylfonylhydrazide,[3] and 2,5-dichlorobenzenesulfonylhydrazide[4] were prepd by standard procedures.

2-Methoxy-3,5-dimethyl- and 2-Chloro-5-carboxybenzenesulfonyl Hydrazide. A soln of 2-methoxy-3,5-dimethyl- and 2-chloro-5-carboxybenzenesulfonyl chloride in EtOH was treated with NH_2NH_2–H_2O (98%) at 0°. It was left at room temp for several hr, when crystals of the hydrazide were obtd. Recrystn from EtOH gave a colorless product, mp 116–117°. 2-MeO-3,5-Me_2 deriv. *Anal.* ($C_9H_{14}N_2O_3S$) C, H, N. 2-Cl-5-CO_2H deriv, mp 87°. *Anal.* ($C_7H_7ClN_2O_4S$) C, H, N.

N′-Substituted Arylsulfonyl-3,5-dimethyl-4-arylazopyrazoles. A hot soln of arylsulfonylhydrazide (0.01 mole) in EtOH (30 ml)

Table I. N^1-Arylsulfonyl-3,5-dimethyl-4-arylazopyrazoles



No.	R_1	R_2	Yield, %	Mp, °C	Color[a]	Formula[b]
1	3-NO_2-4-OMe	2-Cl	65	168–169	Ly	$C_{18}H_{16}ClN_5O_5S$
2	3-NO_2-4-OMe	4-OMe	95	194–195	y	$C_{19}H_{19}N_5O_6S$
3	3-NO_2-4-OMe	4-NO_2	80	167–168	O	$C_{18}H_{16}N_6O_7S$
4	3-Cl-4-OMe	2-Cl	65	150–151	Y	$C_{18}H_{16}Cl_2N_4O_3S$
5	3-Cl-4-OMe	2-NO_2	76	224–225	R	$C_{18}H_{16}ClN_5O_5S$
6	3-Cl-4-OMe	4-OMe	70	161–162	Y	$C_{19}H_{19}ClN_4O_4S$
7	2-OMe-5-Cl	2-NO_2	80	200–201	R	$C_{18}H_{16}ClN_5O_5S$
8	2,5-Cl	2-NO_2	90	190–191	DBn	$C_{17}H_{13}Cl_2N_5O_4S$
9	2-Cl-5-COOH	2-NO_2	96	220–221	BR	$C_{18}H_{14}ClN_5O_6S$
10	2-OMe-3,5-Me	4-OMe	96	154–155	Py	$C_{21}H_{24}N_4O_4S$

[a] B, brick; Bn, brown; D, dark; L, light; O, orange; P, pale; R, red; Y, yellow. [b] All compds were analyzed for C, H, N, S.

Table II. Biological Activities of N^1-Arylsulfonylpyrazoles

	% activity at highest tested dosage[b]							
	In Vivo				*In Vitro*			
	Mice				Manure			
No.[a]	Tg	N	C	O	R/Lv/Ad	Hc/Ts	F	Dose, ppm
1		0	0	60	75/0/0	100/100	0	100
2	0	0	0	0				400 mg/kg
3	0	0	0	0	50/0/0	100/100	0	100 mg/kg
4		0		0	0/0/0	60/90	0	100
5	0	0	0	0	0/0/0	0/50	0	100, 400 mg/kg
6	0	0	0	50				400 mg/kg
7	0				0/0/0	50/50	0	100
8	0				0/0/0	0/50	0	100
9	0	0	0	50				400 mg/kg
10	0	0	0	0				100

[a] Same as Table I. [b] Tg, *Toxoplasma gondii*–RH strain in mice prevention (of mortality); N, nematodes (*trichostrongyles* in mice); C, cestoses (tapeworms in mice); O, oxyurids (in mice); R, % repellency (of face fly oviposition); Lv, % contact activity on face fly larvae (prevention of pupation); Ad, % kill of adult face flies and/or pupae which fail to hatch; Hc, % inhibition of *Haemonchus contorus* larvae development; Ts, % inhibition of *Trichostorgylus spp.* larvae development; F, % inhibition of fungus growth.

*To whom inquiries should be addressed at Harvard University Medical School, Laboratory for Carbohydrate Research, Massachusetts General Hospital, Boston, Mass. 02114.

†This work was supported by a grant from The Chemical Society, London. Taken from the dissertation submitted by N. K. in partial fulfillment of the requirements for a Master of Science degree, University of Roorkee, Roorkee, India, 1971.