Table 1.[12] Inhibition of Uptake of (−)-H^3-Norepinephrine (10 ng/ml, 28.5 nCi/ml, 30-min Incubation) by the Drugs in the Rat Vas Deferens

Drug	Concn, *M*	Uptake of (−)-H^3-NE with SEM, cpm/tissue		% of control uptake with SEM	Approx rel activity[c]
		Control	With inhibitor[b]		
Control[a]		3332 ± 150			
1	7×10^{-5}		1171 ± 129	35 ± 3	
Control[a]		3118 ± 155			
2	1×10^{-4}		2158 ± 93	70 ± 4	
Control[a]		3167 ± 441			
2	1×10^{-3}		633 ± 26	21 ± 2	1 > 2 (7:1)
Control[a]		3660 ± 437			
5	5×10^{-4}		1136 ± 105	31 ± 1	1 > 5 (7:1)
Control[a]		3577 ± 333			
6	1×10^{-5}		1347 ± 14	38 ± 3	
Control[a]		3900 ± 321			
6	1×10^{-4}		538 ± 30	14 ± 3	
Control[a]		3500 ± 177			
7	3×10^{-4}		2539 ± 327	72 ± 6	6 > 7 (662:1)

[a]Contralateral tissue was used as control. [b]Incubation time, 15 min. [c]Determined from the graphic plot.

norephinephrine (28.5 nCi/ml, 10 ng/ml for 30 min) except the experimental tissue was incubated for 15 min with the inhibitor of the neuronal uptake prior to the addition of (−)-H^3-norephinephrine. The extraneuronal radioactivity was cleared by washing the tissues for 5 min in two volumes of the Kreb's solution. The tissue was blotted and weighed and the radioactivity was extracted with 2 ml of perchloric acid (0.4 *N*). The supernatum after centrifugation was counted in 13 ml of Aquasol. The vials were counted in a liquid scintillation spectrophotometer.

The tests were repeated three times, and data are reported as mean with the SEM. Since the weights of the contralateral tissues do not deviate more than 4 mg, the uptake of (−)-H^3-norepinephrine is expressed per tissue. It is assumed that liberation of endogenous norepinephrine by these compounds does not affect the relative uptake of (−)-H^3-norepinephrine. Ideally, ID_{50} should be used to determine the relative catecholamine inhibitory effects of drugs. However, the quantity of the material at our disposal was too small to do so. The details of the quantification will be examined in the future. The relative potency was obtained by semilog plot.

trans-3-Phenyl-2-methylazetidin-3-ol (1). The method described by Hortmann and Robertson[9] was employed in preparing 1. The HCl salt of 1 was prepared and recrystallized from $CHCl_3$, mp 179–180°. *Anal.* ($C_{10}H_{14}NOCl$) C, H, N.

trans-3-Phenyl-2-methyl-1-*p*-toluenesulfonamidoazetidin-3-ol (3). To a stirred solution of 2.3 g (0.012 mol) of the HCl salt of 1 in 25 ml of pyridine was added 2.6 g (0.013 mol) of TsCl. The resulting mixture was allowed to stand 48 hr at room temperature. The yellow mixture was then poured into 40 ml of ice H_2O and stirred for 30 min. The resulting white solid was removed by filtration. The white solid was then taken up in $CHCl_3$, dried (Na_2SO_4), and evaporated to give a white solid (3.5 g, 92%). A portion was crystallized from C_6H_6 giving a white solid: mp 160°; nmr ($CDCl_3$) δ 0.87 (d, 3, J = 6.5 Hz), 2.46 (s, 3), 2.63 (s, 1), 3.5–4.3 (m, 3), 7.1–7.9 (m, 9). *Anal.* ($C_{17}H_{19}NO_3S$) C, H, N.

cis-3-Phenyl-2-methyl-1-*p*-toluenesulfonamidoazetidin-3-ol (4). A mixture of 2 g (6.3 mmol) of sulfonamide 3, 2.06 g of MsCl, and 40 ml of pyridine was maintained at 5° for 72 hr. The mixture was then poured into ice H_2O and stirred overnight. The resulting white precipitate was removed and then taken up in $CHCl_3$. The $CHCl_3$ solution was dried (Na_2SO_4) and evaporated to give 1.8 g of an epimeric mixture of 3 and 4 in a ratio of 3:7 using nmr. The mixture was taken up in 30 ml of C_6H_6 and allowed to sit overnight at room temperature. Clear plate-like crystals of pure 4 (980 mg, 49%) were isolated: mp 138–139°; nmr ($CDCl_3$) δ 1.40 (d, 3, J = 6.5 Hz), 2.45 (s, 3), 3.28 (s, 1), 3.91 (s, 2), 4.16 (q, 1, J = 6.5 Hz), 6.8–7.5 (m, 7), 7.65–7.9 (m, 2). *Anal.* ($H_{17}H_{19}NO_3S$) C, H, N.

cis-3-Phenyl-2-methylazetidin-3-ol (2). Compound 4 (500 mg, 1.58 mmol) was placed in 10 ml of THF and to this was added 500 mg (14 mmol) of $LiAlH_4$ and the mixture was stirred 18 hr at room temperature. The reaction mixture was then carefully decomposed by adding wet ether, followed by water. The solid material was removed by filtration and washed with THF. The THF solution was then dried (Na_2SO_4) and evaporated *in vacuo* to give a white solid. The solid was taken up in ether and 116 mg (45%) of pure 2 was isolated: mp 133°; nmr ($CDCl_3$) δ 1.31 (d, 2, J = 6.5 Hz), 3.54 (d, 1, J = 9 Hz), 3.68 (s, 2, OH and NH), 4.00 (d, 1, J = 9 Hz), 4.20 (q, 1, J = 6.5 Hz), 7.1–7.6 (m, 5). *Anal.* ($C_{10}H_{13}NO$) C, H, N.

Acknowledgment. The financial support of the project by the National Institutes of Health Grants NS09350, GM-17859 and HL-12215 is gratefully acknowledged. Excellent technical assistance was provided by Mrs. Ofilia Hernandez. We thank Dr. Carl Kaiser of the Smith Kline & French Laboratories for the *cis*- and *trans*-2-phenylcyclopropylamines.

References

(1) A. S. V. Burgen and L. L. Iversen, *Brit. J. Pharmacol.*, 25, 34 (1965).
(2) T. Ban and T. Fujita, *J. Med. Chem.*, 12, 353 (1969).
(3) A. I. Salama, J. R. Insalaco, and R. A. Maxwell, *J. Pharmacol. Exp. Ther.*, 178, 474 (1971).
(4) A. S. Horn and S. H. Snyder, *ibid.*, 180, 523 (1972).
(5) P. N. Patil and J. B. Lapidus, *Ergeb. Physiol., Biol. Chem. Exp. Pharmacol*, 66, 213 (1972).
(6) E. E. Smissman and W. H. Gastrock, *J. Med. Chem.*, 11, 860 (1968).
(7) E. E. Smissman and G. S. Chappell, *ibid.*, 12, 429 (1969).
(8) W. L. Nelson and D. D. Miller, *ibid.*, 13, 807 (1970).
(9) A. G. Hortmann and D. A. Robertson, *J. Amer. Chem. Soc.*, 94, 2758 (1972).
(10) R. B. LaCount and C. E. Griffin, *Tetrahedron Lett.*, 1549 (1960).
(11) E. Gold, *J. Amer. Chem. Soc.*, 93, 2793 (1971).
(12) M. Kulka and R. H. Manske, *J. Org. Chem.*, 17, 1501 (1952).

Some Anticonvulsant and Cardiovascular Effects of Substituted Thiazolidones†

S. Nagar, H. H. Singh, J. N. Sinha, and Surendra S. Parmar*

Department of Pharmacology & Therapeutics, King George's Medical College, Lucknow University, Lucknow-3, India.
Received April 19, 1972

Diverse biological properties exhibited by substituted thiazolidones include hypnotic[1] and local anaesthetic[2] activities. The effectiveness of 2-(4-chlorophenyl)-3-methyl-4-thiazolidone and 2-(2-furyl)-3-methyl-4-thiazolidone to afford protection against pentylenetetrazol-induced seizures[3] has also been reported. These observations prompted us to synthesize 2-substituted-imino-3-substituted-5-carboxymethyl-4-thiazolidones and to evaluate their anticonvulsant activity, their effects on resting blood pressure, and their ability to selectively inhibit NAD-dependent oxidations.[4]

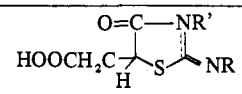
†This investigation was supported with the financial assistance obtained from the Indian Council of Medical Research, New Delhi.

Table I. 1,3-Disubstituted Thiocarbamides, RNHCSNHR'

No.	R	R'	Yield, %	Mp, °C	Formula	Analyses
1	Cyclopentyl	C_6H_5	70	173–175	$C_{12}H_{16}N_2S$	C, H, N
2	Cyclopentyl	4-ClC_6H_4	55	179–180	$C_{12}H_{15}ClN_2S$	C, H, N
3	Cyclopentyl	4-BrC_6H_4	66	174	$C_{12}H_{15}BrN_2S$	C, H, N
4	Cyclopentyl	4-IC_6H_4	50	172–173	$C_{12}H_{15}IN_2S$	C, H, N
5	Cyclopentyl	2-$CH_3C_6H_4$	70	68–70	$C_{13}H_{18}N_2S$	C, H, N
6	Cyclopentyl	3-$CH_3C_6H_4$	62	80	$C_{13}H_{18}N_2S$	C, H, N
7	Cyclopentyl	4-$CH_3C_6H_4$	70	108	$C_{13}H_{18}N_2S$	C, H, N
8	Cyclopentyl	2-$CH_3OC_6H_4$	50	114	$C_{13}H_{18}N_2OS$	C, H, N
9	Cyclopentyl	4-$CH_3OC_6H_4$	55	107–109	$C_{13}H_{18}N_2OS$	C, H, N
10	Cyclopentyl	Cyclohexyl	75	173–175	$C_{12}H_{22}N_2S$	C, H, N
11[a]	Cyclohexyl	C_6H_5	72	148–150		
12	Cyclohexyl	4-ClC_6H_4	73	177–178	$C_{13}H_{17}ClN_2S$	C, H, N
13	Cyclohexyl	4-BrC_6H_4	65	169	$C_{13}H_{17}BrN_2S$	C, H, N
14	Cyclohexyl	4-IC_6H_4	75	169–170	$C_{13}H_{17}IN_2S$	C, H, N
15	Cyclohexyl	2-$CH_3C_6H_4$	60	120	$C_{14}H_{20}N_2S$	C, H, N
16	Cyclohexyl	3-$CH_3C_6H_4$	62	110–112	$C_{14}H_{20}N_2S$	C, H, N
17	Cyclohexyl	4-$CH_3C_6H_4$	55	95	$C_{14}H_{20}N_2S$	C, H, N
18	Cyclohexyl	2-$CH_3OC_6H_4$	66	91	$C_{14}H_{20}N_2OS$	C, H, N
19	Cyclohexyl	3-$CH_3OC_6H_4$	60	112	$C_{14}H_{20}N_2OS$	C, H, N
20[a]	Cyclohexyl	4-$CH_3OC_6H_4$	71	133–134		
21[b]	Cyclohexyl	Cyclohexyl	82	180		

[a] K. N. Campbell, B. K. Campbell, S. J. Patelski, *Proc. Indiana Acad. Sci.*, 53, 119 (1963). [b] D. Martin and W. Mucke, *Monatsber. Deut. Akad. Wiss. Berlin*, 6, 362 (1964).

Table II. 2-Substituted-imino-3-substituted-5-carboxymethyl-4-thiazolidones



No.	R	R'	Yield, %	Mp, °C	Formula	Analyses
22	Cyclopentyl	C_6H_5	50	132–133	$C_{16}H_{18}N_2O_3S$	C, H, N
23	Cyclopentyl	4-ClC_6H_4	42	145–146	$C_{16}H_{17}ClN_2O_3S$	C, H, N
24	Cyclopentyl	4-BrC_6H_4	53	155	$C_{16}H_{17}BrN_2O_3S$	C, H, N
25	Cyclopentyl	4-IC_6H_4	54	152–153	$C_{16}H_{17}IN_2O_3S$	C, H, N
26	Cyclopentyl	2-$CH_3C_6H_4$	44	132	$C_{17}H_{20}N_2O_3S$	C, H, N
27	Cyclopentyl	3-$CH_3C_6H_4$	45	126	$C_{17}H_{20}N_2O_3S$	C, H, N
28	Cyclopentyl	4-$CH_3C_6H_4$	40	159–160	$C_{17}H_{20}N_2O_3S$	C, H, N
29	Cyclopentyl	2-$CH_3OC_6H_4$	50	127–128	$C_{17}H_{20}N_2O_4S$	C, H, N
30	Cyclopentyl	4-$CH_3OC_6H_4$	48	197	$C_{17}H_{20}N_2O_4S$	C, H, N
31	Cyclopentyl	Cyclohexyl	46	113–115	$C_{16}H_{24}N_2O_3S$	C, H, N
32	Cyclohexyl	C_6H_5	60	203	$C_{17}H_{20}N_2O_3S$	C, H, N
33	Cyclohexyl	4-ClC_6H_4	50	198	$C_{17}H_{19}ClN_2O_3S$	C, H, N
34	Cyclohexyl	4-BrC_6H_4	50	204	$C_{17}H_{19}BrN_2O_3S$	C, H, N
35	Cyclohexyl	4-IC_6H_4	48	222–223	$C_{17}H_{19}IN_2O_3S$	C, H, N
36	Cyclohexyl	2-$CH_3C_6H_4$	54	159	$C_{18}H_{22}N_2O_3S$	C, H, N
37	Cyclohexyl	3-$CH_3C_6H_4$	55	175–177	$C_{18}H_{22}N_2O_3S$	C, H, N
38	Cyclohexyl	4-$CH_3C_6H_4$	49	198	$C_{18}H_{22}N_2O_3S$	C, H, N
39	Cyclohexyl	2-$CH_3OC_6H_4$	45	168	$C_{18}H_{22}N_2O_4S$	C, H, N
40	Cyclohexyl	3-$CH_3OC_6H_4$	47	142	$C_{18}H_{22}N_2O_4S$	C, H, N
41	Cyclohexyl	4-$CH_3OC_6H_4$	46	195	$C_{18}H_{22}N_2O_4S$	C, H, N
42	Cyclohexyl	Cyclohexyl	52	174	$C_{17}H_{26}N_2O_3S$	C, H, N

Chemistry. 1,3-Disubstituted thiocarbamides were prepared by refluxing an equimolar quantity of cyclopentylamine-cyclohexylamine and different isothiocyanates in absolute ethanol. These thiocarbamides when refluxed with maleic anhydride in acetone gave 2,3-disubstituted-5-carboxymethyl-4-thiazolidones.[5]

Experimental Section

The melting points were taken in open capillary tubes with a partial immersion thermometer and are uncorrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical value.

1,3-Disubstituted Thiocarbamides. A mixture of substituted isothiocyanate (0.01 mol) and cyclopentylamine-cyclohexylamine (0.01 mol) in 15–20 ml of absolute EtOH was refluxed on a steam bath under anhydrous conditions. After the excess of EtOH was removed by distillation, the resulting syrupy mass was kept over anhydrous $CaCl_2$ in a desiccator for 48 hr. The crude product which separated out was collected by filtration and recrystallized form EtOH (Table I).

2,3-Disubstituted-5-carboxymethyl-4-thiazolidones. A mixture of 1,3-disubstituted thiocarbamide (0.005 mol) and maleic anhydride (0.005 mol) in 20–25 ml of anhydrous Me_2CO was refluxed on a steam bath under anhydrous conditions for 18–20 hr. Excess of the solvent was removed by distillation. The crude product which separated out on cooling was collected by filtration and recrystallized from EtOH (Table II).

Biological Methods

Studies on Gross Behavior. The study was carried out in mice (20–25 g) according to the scheme outlined by Irwin.[6]

Anticonvulsant activity was determined against pentylenetetrazol-induced seizures according to the method reported earlier.[7]

Effect on Blood Pressure (Cardiovascular Effects). The present study was carried out on adult cats of either sex

Table III. Anticonvulsant and Cardiovascular Effects of Substituted Thiazolidones

Compd	Approximate LD_{50}, mg/kg ip	Fall in resting blood pressure[a]	Cardiovascular effects[c]				Anticonvulsant[b] activity	
			Effect on CO response	Effect on Ad response	Effect on Ach response	Effect on 5-HT response	% protection	24-hr mortality
22	325	+++t	–	–		–	0	20
23	150	++t	–	–	–	–	0	100
24	175	+++t	–	–		–	0	100
25	200	+++t	–	–	–	–	0	60
26	300	+++t		–	–	–	80	0
27	300	+++t	–	–	–	–	30	20
28	150	+++t	–	–	–	–	20	60
29	400	+++t	–	–		–	60	40
30	300	+++t	–	–	–	–	30	20
31	100	+++t	–	–		–	80	0
32	300	+++t	–	–	–	–	20	50
33	50	+++t	–	–	–	–	20	40
34	300	+++l		–	–	–	0	20
35	100	+t	–	–	–	–	40	40
36	200	+t	–	–	–	–	40	60
37	150	+t	–	–	–	–	0	80
38	200	+t	–	–	–	–	20	80
39	150	+t	–	–	–	–	0	100
40	300	+t	–	–	–	–	40	60
41	300	+++t	–	–	–	–	0	40
42	200	+t	–	–	–	–	0	20

[a]Fall in resting blood pressure at 1/20 of LD_{50} dose were <20 mm, +; 20–30 mm, ++; 30–40 mm, +++; transient effect, t; lasting effect (2–3 hr), l; bilateral carotid occlusion, CO; adrenaline, Ad; acetylcholine, Ach; 5-hydroxytryptamine, 5-HT; no effect. Values of the range of fall in resting blood pressure have been obtained from three separate experiments for each compound. [b]Dose 1/5 of the LD_{50}. [c]Adrenaline, acetylcholine, and 5-hydroxytryptamine were used in single doses of 1.0, 0.5, and 1.0 μg/kg, respectively.

weighing 2–4 kg. The animals were anaesthetized with sodium pentobarbital (30 mg/kg iv), vagotomized, and maintained on positive-pressure artificial respiration. The systemic blood pressure was recorded from one of the common carotid arteries through a manometer on smoked kymograph paper. The endwelling polythene cannula was put in one of the femoral veins for injection of drugs and saline. Some of the compounds were dissolved in propylene glycol. In such cases the amount of propylene glycol injected at one time was limited to 0.5 ml and responses to 0.5 ml of solvent were used as controls. The effect of these thiazolidones was studied on resting blood pressure, pressor responses to bilateral carotid occlusion, and adrenaline and depressor responses to acetylcholine and 5-hydroxytryptamine.

Biological Results and Discussion. The results of the biological activity are summarized in Table III. Studies on gross behavior in mice have indicated that all thiazolidones (**22–42**) exhibited depression of the CNS as was evident from reduced locomotor activity, ataxia, hind limb weakness, and loss of righting reflex. Cyclohexylimino derivatives (**32–41**) as compared to cyclopentylimino derivatives (**22–31**) were found to be more active. Anticonvulsant activity of cyclopentylimino derivatives (**22–31**), as reflected by the protection afforded against pentylenetetrazol-induced seizures, was found to be greater than the cyclohexylimino derivatives (**32–42**).

Studies on the cardiovascular system showed that all substituted thiazolidones induced hypotension of varying degree. The duration of hypotensive activity was less than 15 min with most of these compounds. Compound **26**, in addition, potentiated the bilateral carotid occlusion induced pressure responses. Some of these thiazolidones (**22**, **24**, **29**, **31**) potentiated acetylcholine-induced depressor response. 2-Cyclohexylimino-3-(4-bromophenyl)-5-carboxymethyl-4-thiazolidones (**34**) elicited a hypotensive response of 30–40 mm which lasted for approximately 3 hr. This compound (**34**) inhibited the bilateral carotid occlusion induced pressor responses without affecting the responses to adrenaline, acetylcholine, and 5-hydroxytryptamine. These observations have indicated hypotensive activity of a degree which warrants further detailed study of 2-cyclohexylimino-3-(4-bromophenyl)-5-carboxymethyl-4-thiazolidone.

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

References

(1) W. J. Doran and H. A. Shoule, *J. Org. Chem.*, 3, 193 (1938).
(2) A. R. Surrey, *J. Amer. Chem. Soc.*, 71, 3105, 3354 (1949).
(3) H. D. Troutman and L. M. Long, *ibid.*, 70, 3436 (1948).
(4) S. S. Parmar, C. Dwivedi, A. Chaudhari, and T. K. Gupta, *J. Med. Chem.*, 15, 99 (1972).
(5) J. P. Trivedi, S. J. Contractor, and I. D. Shah, *J. Indian Chem. Soc.*, 43, 265 (1966).
(6) S. Irwin in "Evaluation of Drug Activities: Pharmacometrics," Vol. I, D. R. Laurence and A. L. Bacharach, Ed., Academic Press, London, 1964, p 33.
(7) S. Nagar and S. S. Parmar, *Indian J. Pharm.*, 33, 61 (1971).