LETTER TO THE EDITOR

ANTICONVULSANT AND ANALGESIC ACTIVITY OF 1, 2, 4-THIADIAZOLES. II

Sir,

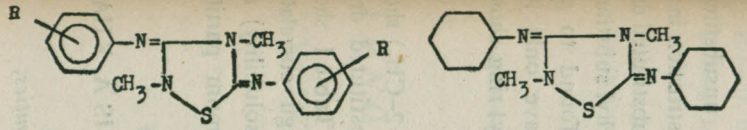
(Received on April, 15, 1988)

A variety of five membered heterocyclic compounds have recently been synthesized as acetazolamide analogues and screened for anticonvulsant activity. Recently Chapleo *et al.* (1, 2, 3) and Stillings *et al.* (7) reported on potent anti-convulsant properties of substituted 1, 3, 4-thiadiazoles in rats and mice against electrically and chemically induced seizures. This prompted us to synthesize a few 1, 2, 4-thiadiazoles (which are isomeric with 1, 3, 4-thiadiazoles) and test their anticonvulsant and analgesic activities, along with their safety indices.

A total of eleven analogues were prepared (Table I) according to method described by Christophersen *et al* (4). They were soluble in chloroform, polyethyleneglycol 200 and in hot ethanol. Albino rates (CF) of either sex (100-200 g) were used in all experiments. All the drugs were given in a dose of 4 *mg/kg* as solutions in polyethyleneglycol 200. Diphenyl hydantoin (SIGMA; ip) and phenobarbitone sodium (IDPL; ip) were used as standards for work on anticonvulsant activity. They were given as aqueous solutions (ip). Control groups received either polyethylene glycol 200 or normal saline (0.5 *ml*, as the case may be). Morphine sulphate was the standard in analgesiometry (control animals received only normal saline). There were 10 animals per group.

Seizures were induced by DC (see 8; 150 mA, for 0 2 sec) delivered through a pair of corneal electrodes, using a Technoconvulsiometer. The presence or absence of hind limb extensor was taken as the end point, showing protection or a lack of it. Drugs were administered (ip) to groups of animals 24 hr after initial screening for convulsion, and their effect determined after 45 min in MES test. Convulsions were also induced chemically. Strychnine hydrochloride (IDPL, 4 *mg/kg* sc) was administered in all groups 45 min after 'drug' administration, and the animals observed for another 45 min for convulsions. Pentylene tetraole (BOEHRINGER-KNOLL; 100 *mg/kg*, sc) and picrotoxin (SISCO LABS; 14.4 *mg/kg*, sc) were

TABLE I : Anticonvulsant (Electro-shock) and analgesic activity of 1, 2, 4-thiadiazoles



Compounds I — X Compound — XI

Fig. 1 : Structure of derivatives of 1, 2, 4-thiadiazoles.

Compd. No.	*Treatment R*	*Partition coefficient 25°C; pH 7.4 ($CHCl_3$: Phosphate buffer system)*	*Anticonvulsant activity (% Protection) n=10*	*Analgesic activity Latent period of tail flick response (sec) Mean±SEM (n=10)*	
				Control	*Treated*
Saline	—	—	0	—	—
I	H	2.79	40	8.45±0.294	10.20±0.555*
II	2-CH_3	1.38	10	8.68∓0.151	12.71±0.312***
III	3-CH_3	6.91	60*	8.70±0.173	8.38±0.229
IV	4-CH_3	8.32	80**	9.46±0.323	16.05±1.21*
V	2-Cl	0.58	0	6.45±0.496	6.81±0 206
VI	3-Cl	0.81	0	9.59±0.476	14.00±1.025**
VII	4-Cl	2.36	10	4.33±0.168	9.47±0.813**
VIII	4-Br	2.45	10	7.61±0.523	11.36±0.324**
IX	2-OCH_3	0.69	30	8.16±0.326	11.16±0.649**
X	4-OCH_3	3.10	40	8.40±0.235	9.97±0.615*
XI	—	6.87	60*	8.29±0.367	8.31±0.260
	Diphenyl hydantoin sodium		60*		
	Phenobarbitone sodium		100***		
	Morphine sulphate			7.18±0.238	13.89±0.361***

Drugs were given (ip); see text for details.

* P<0.05 n=number of animals

** P<0.01

**+ P<0.001 Chi - square test for anticonvulsant and 't' test for analgesic activity.

also used as chemoconvulsants in some experiments. The results were analysed by Chi-square test. The ED_{50} and LD_{50} were calculated by making use of the probit transformation (5).

Analgesic studies were performed using thermal stimulus technique as described by Kendall *et al.* (6). The tail was gently immersed into water kept at 50°C and the time taken for the withdrawl of tail was noted. Animals showing the flick time in range of 3 to 10 sec only were selected. All treatments (4 *mg/kg*, or morphine, 10 *mg/kg*, ip) were administered to groups of animals. After 30 min tail flick time was determined again. The results were analysed by student's 't' test.

Most of the compounds exhibited anti-MES activity. The parent unsubstituted compound (I) was found to give 40% protection at a dose of 4 *mg/kg* (ip). Substitution in the benzene ring showed considerable variation in the activity. The meta methyl substituted drug (III, ED_{50}=4.17 *mg/kg*, LD_{50}=34.52 *mg/kg* with safety index 8.28) and para methyl substituted drug (IV, ED_{50}=1.04 *mg/kg*, LD_{50}=19.84 *mg/kg* with safety index 19 08) were found to give 60% and 80% protection respectively, while ortho substituted (II) drug gave only 10% protection. The drug (XI) in which benzene ring was replaced with a cyclohexyl ring showed 60% protection (ED_{50}=5.25 *mg/kg*, LD_{50}=25.36 *mg/kg* and safety index 4.83).

Most of the compounds of the series were analgesic. Compound II (R=2-CH_3) shows very highly significant analgesic value ($P<0.001$). The chloro and bromo substituted drugs Compounds VI, VII, VIII and IX) show highly significant analgesic activity. Table I shows the potency rating in comparison with morphine at a dose of 10 *mg/kg*. A high correlation coefficient (r=0.99, n=11) was obtained between partition coefficient (lipid solubility) and anticonvulsant activity (percentage protection). The compound with maximum partition coefficient showed maximum activity.

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