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LETTER TO THE EDITOR

SYNTHESIS AND BIOLOGICAL ACTIVITIES OF 2, 4-DIETHYL-3, 5-DIARYL IMINO-1, 2, 4-THIADIAZOLIDINES. III*

Sir,

(Received on August 28, 1989)

Pandeya and Khan reported anticonvulsat property of 1, 2, 4-thiadiazolidines (1), synthesis of which was prompted from reports on 1, 3, 4). This report deals with anticonvulsant and analgestic activity of some further derivatives of 1, 2, 4-thiadiazoles. The essential difference in earlier series and the present series compounds is that replacement of a methyl group with that of more lipophilic ethyl group in the basic ring structure, which may be beneficial in CNS activity.

The methodology of the work elucidation and analysis of results in anti-MES and analgesiometry has already been presented in details earlier (1).

Most of the compounds exhibited anti-MES activity. The parent unsubstituted compound (I) was found to give 30% protection at a dose of 4 mg/kg (ip). Substitution in the benzene ring of the thiadiazolidine ring showed variation in the activity. The meta methyl substituted compound (III, ED_{50}=2.818 mg/kg, LD_{50}+34.50 mg/kg with protective index 12.24), paramethyl substituted compound (IV, ED_{50}=2.137 mg/kg, LD_{50}=28.18 mg/kg with protective index 13.19) and para ethoxy substituted compound (XIII, ED_{50}=2.511 mg/kg, LD_{50}=17.78 mg/kg with protective index 7.08) were fonnd to give 60%, 80% and 60% protection respectively. The compound XIV in which bengene ring was replaced with a cyclohexyl rings showed 60% (ED_{50}=3.31 mg/kg, LD_{50}=25.35 mg/kg and protective index 7.66).

Most of the compounds of the series were analgesic. Compound IV (R=4-CH_3), X (R=2-OCH_3) and XI (R=3-OCH_3), showed very highly significant analgesic value ($P<0.001$). The parent unsubstituted compound I (R=H) and compound III (R=3-CH_3) showed highly significant analgesic activity. The para chloro and para bromo substituted compounds, VII and VIII respectively showed significant analgesic activity. Table I shows the potency rating in comparison with morphine at a dose of 10 mg/kg.

A significantly correlation coefficient, ($r=0.607$; $n=14$) 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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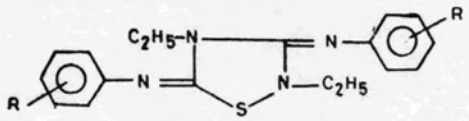
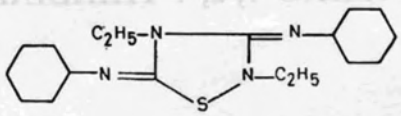


Compounds I - XIII



Compound - XIV

Fig. 1 Structures of derivatives of 1,2,4-thiadiazolidines.

Anti-MES and analgesic activity of 1, 2, 4-thiadiazolidines.

Compound number	*Treatment R*	*Partition coefficient, 30°C; pH7.4 ($CHCl_3$: phosphate) buffer system*	*Anticonvulsant activity (% protection) n=10*	*Analgesic activity, Latent period of tail flick response (Sec) X+SEM (n=10)*	
				Control	*Treated*
Saline	—	—	0	—	—
I	H	1.2	30	10.26 ±0.625	15.31 ±0.532**
II	2-CH_3	8.30	0	6.40 ±0.205	6.92 ±0.236
III	3-CH_3	8.11	60*	5.347±0.057	10.39 ±0.6487**
IV	4-CH_3	6.05	80**	7.205±0.028	8.3 ±0.0428***
V	2-Cl	0.14	0	8.27 ±0.028	8.32 ±0.0091
VI	3-Cl	0.25	0	5.685±0.481	7.48 ±1.0693
VII	4-Cl	1.31	20	6.40 ±0.009	6.44 ±0.0007*
VIII	4-Br	2.33	30	6.43 ±0.0003	6.40 ±0.0009*
IX	3-NO_2	0.12	10	6.42 ±0.0576	6.43 ±0.0288
X	2-OCH_3	0.42	0	8.26 ±0.0032	11.50 ±0.2397***
XI	3-OCH_3	1.5	20	8.40 ±0.0283	9.485±0.0009***
XII	4-OCH_3	4.0	40	8.39 ±0.2057	8.40 ±0.2065
XIII	4-OC_2H_5	9.0	60*	8.195±0.0288	8.33 ±0.0375
XIV	—	10.12	60*	5.635±0.6228	7.06 ±1.0361
Diphenylhydontoin sodium.			60	—	—
Phenobarbitone sodium.			100***	—	—
Morphine sulphate.				8.350±0.0289	9.506±0.0009***

Drugs were given (ip); See textfor details
* P<0.05 n=Number of animals
** P<0.01
*** P<0.001 Chi-square test for anticonvulsant; 't' test for other data.

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