SYNTHESIS OF NEW N^3- SUBSTITUTED THIADIAZOLE HYDANTOIN DERIVATIVES AS ACTIVE ANTIEPILEPTIC COMPOUNDS

Dr. Sangeeta Kamthan
Associate Professor, Department of Chemistry
Bareilly College, Bareilly. (UP)
drdk62@yahoo.com

Abstract:
A new series of N^3 – substituted 5-phenyl-1, 3, 4-thiadiazole-2-yl has been synthesized by condensation of different chloro-acetylated thiadiazole nuclei with alkali metal cyanate in presence of quaternary ammonium salt. The rate of reaction was found to be enhanced in presence of a polar solvent.

The compounds were evaluated for anticonvulsant activity. Di-phenyl hydantoin sodium was used as the standard drug.

Two of the compounds showed significant activity, compound V, N^3–(5-p-dimethyl-amino-phenyl-1, 3, 4-thiadiazole -2-yl) hydantoin and compound II, N^3 –5-(p-methoxy-phenyl-1, 3, 4-thiadiazole -2-yl) hydantoin were found to show potent activity.

Key Phrases: epilepsy, anticonvulsant compounds, structure-activity relationship.

Introduction:

Epilepsy influences around 1% of the total populace around the world. Because of the reality all antiepileptic drugs (AEDs) make a few unwanted side effects and around 30% of the epileptic patients are not seizure-free with AEDs, there is yet an emergent requirement for the improvement of more compelling and more secure AEDs.

Therefore, the quest for antiepileptic compound with more specific action and lower toxicity keeps on being an area of escalated interest in medicinal chemistry.

Frank et.al. (1926) [1] portrayed the importance of N^3 – substituted hydantoins as agents with desirable anticonvulsive activity.

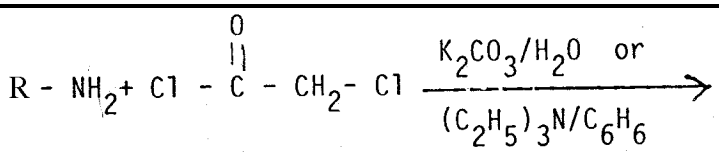
Later, Maffi et.al. (1858) [2], Clarkson (1964) [3] and Barnish et.al. (1977) [4] synthesized substituted thiadiazoles which were found to be effective against convulsive seizures. It was, thus, thought worthwhile to synthesize some new thiadiazole hydantoin derivatives by substitution in the hydantoin ring at N^3 – position (Orazi et.al.1974) [5] which might be demonstrated to be more potent and specific, and perhaps liberated from seizures and toxicity.

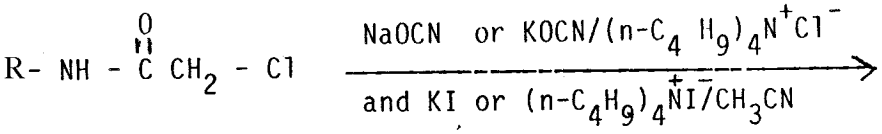
The present communication features the properties of new derivatives enriched with anticonvulsive properties and lower the level of unfortunate side effects.

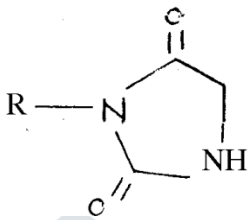
Material and Methods:

Synthesis

N^3 substituted hydantoin derivatives were synthesized by the method of Kim and Kwon (1982) [6] in two stages. First, chloro-acetylated heterocyclic mixtures were prepared by treating the heterocyclic compounds with chloro-acetyl chloride in dry benzene. In second stage, chloro-acetylated derivatives were treated with potassium cyanate in presence of catalytic amount of tetra-n-butyl-ammonium iodide and potassium-iodide containing a polar solvent, acetonitrile. The general sequence of the chemical reaction may be depicted as follows:







Antiepileptic activity:

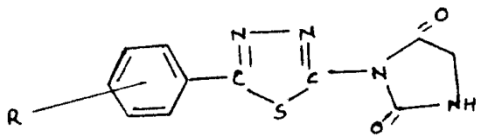
Male albino mice weighing 20-25 mg were used in the present study. They were maintained at an ambient temperature of 22 ± 1℃ and had food and water ad.libitum. The mice were divided into groups of six animals each except otherwise mentioned. The test compounds were dissolved in polysorbate (Tween 80) and diluted with distilled water and were injected i.p.in a dose of 100 mg/kg to the mice. One group received standard drug, Di-phenyl hydantoin sodium in a dose of 25 mg/kg i.p. The control group received vehicle only. The animals were observed for behavioral changes, if any, up to 1 hour of drug administration.

The anticonvulsant activity was studied by maximum electro-shock seizures (MES).The electro-shock (48mA,0.2 sec.) was delivered 1 hr. after the drug administration through a convulsiometer (Techno) by using ear electrodes according to the method of Swinyard et.al.(1952) [7]. After the delivery of shocks, duration of various phases of MES (tonic flexion, tonic extensor and clonus) and of post seizure depression, defined as the time required to regain the righting-reflux (RR), was taken as the index for protection. The statistical significance of the difference in the mean values were calculated by the student's't' test.

Results:

A series of thiadiazole substituted hydantoins were synthesized and their structure, physical and chemical properties are summarized in Table 1.

Table 1.The molecular formula, melting-point & percentage yield of substituted hydantoins of thiadiazole.



S. No.	R	X	Molecule formula	M.P ℃	Yield %
I	5-phenyl-1,3,4-thiadiazole-2-yl	—	$C_{11}H_8N_4O_2S$	245	61
II	5-phenyl-1,3,4-thiadiazole-2-yl	p-methoxy	$C_{12}H_{10}O_3N_4OS$	242	67
III	5-phenyl-1,3,4-thiadiazole-2-yl	p-ethoxy	$C_{13}H_{12}N_4O_3S$	260	68
IV	5-phenyl-1,3,4-thiadiazole-2-yl	p-hydroxy	$C_{11}H_8N_4O_3S$	242	64
V	5-phenyl-1,3,4-thiadiazole-2-yl	p-dimethylamino	$C_{13}H_{13}N_5O_2S$	259	65.4
VI	5-phenyl-1,3,4-thiadiazole-2-yl	p-chloro	$C_{11}H_7N_4O_2SCl$	248	60
VII	5-phenyl-1,3,4-thiadiazole-2-yl	o-chloro	$C_{11}H_7N_4O_2SCl$	240	56
VIII	5-phenyl-1,3,4-thiadiazole-2-yl	p-bromo	$C_{11}H_7O_2N_4SBr$	235	58
IX	5-phenyl-1,3,4-thiadiazole-2-yl	o-bromo	$C_{11}H_7N_4O_2SBr$	221	55
X	5-phenyl-1,3,4-thiadiazole-2-yl	p-fluoro	$C_{11}H_7O_2N_4SF$	271	48

The analysis of N, S, Cl, Br and F found and calculated did not differ more than 0.4%

The yield of the compound varied from 48 to 68%. The p-ethoxy derivative showed the maximum yield. Almost all the compounds showed high melting point ranging from 221 to 271^{0}C.

The compounds were evaluated for their anticonvulsant action and were contrasted with the standard medication, Di-phenyl-hydantoin sodium. There was a marked variation in the anticonvulsant activity of N^3 – substituted thiadiazole hydantoins. The results are signified in Table 2.

Table 2. Effect of substituted hydantoins of thiadiazole on components of electro-shock-induced seizures in male albino mice.

Compound No.	No. of Animals	Mean duration in seconds ± SEM			
		Flexor	Extensor	Clonus	Stupor
Vehicle Control	11	2.29 ± 0.16	15.09 ± 1.35	11.80 ± 3.19	53.80 ± 10.06
I	6	3.40 ± 0.15****	7.66 ± 1.74**	7.00 ± 1.46	123.5 ± 32.5*
II	6	4.70 ± 0.56****	3.90 ± 1.74****	5.5 ± 0.82	14.16 ± 3.8***
III	6	5.8 ± 0.68****	3.9 ± 7.84****	9.2 ± 1.01	18.42 ± 5.2***
IV	6	3.84 ± 0.32	13.99 ± 2.61	8.81 ± 2.93	52.26 ± 9.08
V	6	4.2 ± 0.48****	2.98 ± 1.04****	9.11 ± 0.71	18.23 ± 4.91
VI	6	2.81 ± 0.21	12.65 ± 1.23	7.03 ± 1.11	33.16 ± 7.02
VII	6	2.98 ± 0.51	13.04 ± 1.81	7.93 ± 4.24	54.78 ± 9.64
VIII	6	5.82 ± 1.01	15.61 ± 2.08	8.46 ± 5.21	80.16 ± 10.84
IX	6	8.41 ± 2.03	17.84 ± 4.42	9.86 ± 7.24	80.74 ± 11.01
X	6	11.61 ± 5.81	21.64 ± 5.21	13.62 ± 9.41	91.84 ± 13.41
Diphenyl hydantoin sodium	6	1.63 ± 0.24*	0.00 ± 0.00****	2.20 ± 1.04****	4.73 ± 1.79***

P value in comparison to control group -*P: - < 0.05, **P :-< 0.025, ***P :-< 0.01, ****P: -< 0.001
'a' : Dose of 25 mg/kg i.p

The compound II and V offered significant anticonvulsant activity against electro-shock-induced seizures. However, compounds VII, IX and X did not show any anticonvulsant activity. The compound II and V exhibited maximum anticonvulsant action on extensor component of electro-shock, although the flexor duration was almost same for both the compounds. Compound II had an added advantage of decreased clonus and stupor component ($P < 0.01$).

The mortality rate was almost same in all the compounds as observed after 1 hour and 24 hours of chemo shock induced seizures. The compounds II, V and X offered lowest percent mortality rate in 50% of the animals. Almost all the animals showed tremors and depressant effects.

Compound X has marked irritant effect accompanied by trimerogenic effect.

Diphenyl-hydantoin sodium (25mg/kg) offered total protection against electro-shock- induced seizures. The percent mortality rate was also found to be nil after 1 hour as well as 24 hours of administration.

Discussion:

There was a marked variation in the results of compounds having p-alkoxy, p-dimethyl amino and ortho or para halo-atoms in the heterocyclic nuclei of hydantoins. In general, few have shown moderate anticonvulsant activity as shown in Table 2.

Results have shown that almost all the compounds were active as compared to vehicle control as indicated by decreased duration of extensor component of electro-shock seizure.

Compound V with p-dimethyl amino substitution has significant activity as compared to other derivatives.

The p-methoxy compound (II) is also found to be active but compound V dominates over compound II as it has an added advantage by decreasing the time duration of clonus and stupor ($P < 0.01$) of electro-shock seizures.

The substitution of chlorine atom at para position, compound IV, shows slightly higher anticonvulsant activity as compared to ortho substituted chloro-atom, compound VII, by decreasing the time duration of stupor phase. On the contrary, the ortho and para substituted derivatives of bromine, Compound VIII and IX, does not show any remarkable difference.

The para substituted fluorine compounds were found to be least anticonvulsant and highly toxic as shown by their mortality rate of chemo-shock-induced seizures.

The compound III and V have also found to possess CNS depressant effect, which may be responsible for its anticonvulsant activity.

The order of anticonvulsant effect against electro-shock and chemo-shock-induced seizures was, thus, found to be compound V > II > III.

In conclusion, it is suggested that hydantoins with substituted thiadiazole moiety are moderately anticonvulsants and may represent a starting point to allow a better understanding of antiepileptic therapeutic developments as well as to suggest ideas for designing and synthesizing a novel series of antiepileptic compounds.

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